

102457

SEARCH REQUEST FORM

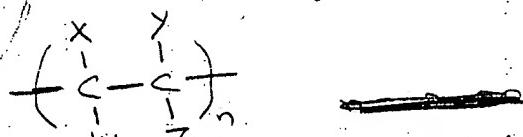
Requestor's Name: Ganapathy Krishnan Serial Number: 09 1937991
 Date: 8/26/03 Phone: 305 - 4837 Art Unit: 1623
Off: 8D08 MR: 8B19

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Search for:

A polymer having the structure:



Wherein X, Y, Z is any substituent including hydrogen. W is a carbohydrate chain. The carbohydrate chains are listed in claim 3.

L1

STAFF USE ONLY

Date completed: 8/29Searcher: HanleyTerminal time: 45Elapsed time: 60CPU time: Total time: Number of Searches: Number of Databases:

Search Site

 STIC CM-1 Pre-S

Type of Search

 N.A. Sequence A.A. Sequence Structure Bibliographic

Vendors

 IG \$450 STN Dialog APS Geninfo SDC DARC/Questel Other



STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact:*

Mary Hale, Information Branch Supervisor
308-4258, CM1-1E01

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* Example: 1610
- *Relevant prior art found, search results used as follows:*
- 102 rejection
 - 103 rejection
 - Cited as being of interest.
 - Helped examiner better understand the invention.
 - Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- Foreign Patent(s)
- Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ *Relevant prior art not found:*

- Results verified the lack of relevant prior art (helped determine patentability).
- Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library CM1-1 Circ Desk



A \equiv carbohydrate polymer
will be indexed by
its monomers

CT = controlled terms
PFT = old, new, "used
for" terms
NT = narrower
term

=> d que 141 text approach

L31 59141 SEA FILE=HCAPLUS ABB=ON PLU=ON MUCOPOLYSACCHARIDES+PFT, NT/CT
 L32 358592 SEA FILE=HCAPLUS ABB=ON PLU=ON VINYL COMPOUNDS+PFT, NT/CT
 L33 33892 SEA FILE=HCAPLUS ABB=ON PLU=ON (HEPARIN OR HEPARAN OR
DERMATAN OR CHONDROITIN)/OBI
 L34 2312 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND L32
 L35 776 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 AND L33
 L36 135 SEA FILE=HCAPLUS ABB=ON PLU=ON L33(L)VINYL
 L37 94 SEA FILE=HCAPLUS ABB=ON PLU=ON L36 AND L35
 L38 92 SEA FILE=HCAPLUS ABB=ON PLU=ON L37 AND PY<2003
 L39 23 SEA FILE=HCAPLUS ABB=ON PLU=ON L38 AND (ETHYLEN? OR ETHENYL?
OR STYREN?)/OBI
 L40 22 SEA FILE=HCAPLUS ABB=ON PLU=ON L38 AND (POLYETHYLEN? OR
POLYETHENYL? OR POLYSTYREN?)/OBI
 L41 39 SEA FILE=HCAPLUS ABB=ON PLU=ON (L39 OR L40) 39 cites

includes the
subheading
glycosaminoglycan
& heparin, dermatan
& chondroitin
derivatives

=> d que 145 Registry approach

L10 159958 SEA FILE=REGISTRY ABB=ON PLU=ON PVIN/PCT \leftarrow polyvinyl polymers
 L11 106205 SEA FILE=REGISTRY ABB=ON PLU=ON PSTY/PCT \leftarrow poly styren " "
 L15 22253 SEA FILE=REGISTRY ABB=ON PLU=ON 7664-93-9/CRN sulfate as a polymer component
 L17 1195 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND OC5/ES \leftarrow ring
 L18 600 SEA FILE=REGISTRY ABB=ON PLU=ON L17 AND ("GLUCOPYRANOSIDE"
OR "GLUCOPYRANOSYL")
 L20 1 SEA FILE=REGISTRY ABB=ON PLU=ON L18 AND (L10 OR L11)
 L21 19 SEA FILE=REGISTRY ABB=ON PLU=ON (L10 OR L11) AND ("DERMATAN"
OR "HEPARIN" OR "HEPERAN" OR "CHONDROITIN")
 L22 536807 SEA FILE=REGISTRY ABB=ON PLU=ON "ETHENYL"
 L23 11 SEA FILE=REGISTRY ABB=ON PLU=ON L22 AND ("DERMATAN" OR
"HEPARIN" OR "HEPERAN" OR "CHONDROIN")
 L24 11 SEA FILE=REGISTRY ABB=ON PLU=ON L23 AND PMS/CI \leftarrow polymer
 L25 20 SEA FILE=REGISTRY ABB=ON PLU=ON L24 OR L21
 L43 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L20
 L44 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L25
 L45 16 SEA FILE=HCAPLUS ABB=ON PLU=ON (L43 OR L44) AND PY<2003 16 cites

=> s 141 or 145

L47 55 L41 OR L45

=> d ibib abs hitstr 1-55

L47 ANSWER 1 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:793739 HCAPLUS
 DOCUMENT NUMBER: 137:284439
 TITLE: Glycosaminoglycan functional polymer and adhesion
protein complexes and applications thereof

P1-2 were not given
they were junks

INVENTOR(S): Yura, Hiroyumi; Ishihara, Masayuki; Saito, Yoshio;
 Ono, Katsuaki; Sato, Masato
 PATENT ASSIGNEE(S): Netech Inc., Japan
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081619	A1	20021017	WO 2002-JP3287	20020402 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.: JP 2001-102883 A 20010402				

AB It is intended to construct environment similar to an extracellular matrix by combining a glycosaminoglycan (GAG) functional polymer with a cell adhesion protein such as collagen, and the GAG functional polymer/protein complexes characterized in that the GAG functional polymer, which has a sugar chain contg. a structure corresponding to at least a part of the basic skeleton of GAG introduced into the main chain of a vinyl-type polymer, is carried on a cell adhesive protein; differentiation and proliferation of cells can be controlled in the novel material and the complexes can be used as cell culture materials and tissue regeneration materials. Heparin-carrying polystyrene (HCPS) was prepd. The HCPS efficiently bound to collagen-coated cell culture plate, thereby retaining the binding of vascular endothelial growth factor (VEGF)165 or fibroblast growth factor (FGF)-2. Human umbilical vein endothelial cells showed a good adherence to the HCPS-bound collagen substrate.

IT 9005-49-6DP, Heparin, reaction products with polystyrene 25322-46-7DP, Chondroitin sulfate C, reaction products with polystyrene
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with proteins for cell adhesion)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-46-7 HCPLUS
 CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

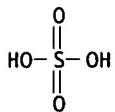
CM 1

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



IT 24967-94-0D, Dermatan sulfate, reaction products with
viny polymers
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glycosaminoglycan-carrying vinyl polymers binding with
proteins for cell adhesion)

RN 24967-94-0 HCPLUS
CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

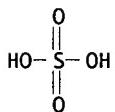
CM 1

CRN 75634-40-1
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
CMF H2 O4 S



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 2 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:332077 HCPLUS
DOCUMENT NUMBER: 136:345860
TITLE: Preparation of hydrophobic multicomponent heparin conjugates for antithrombotic coatings
INVENTOR(S): Byun, Young Ro; Moon, Hyun Tae
PATENT ASSIGNEE(S): Mediplex Corp., S. Korea
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034312	A1	20020502	WO 2000-KR1255	20001103 <--
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

AU 2001011769 A5 20020506 AU 2001-11769 20001103 <--
EP 1333871 A1 20030813 EP 2000-973237 20001103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL
RITY APPLN. INFO.: KR 2000-62668 A 20001024
WO 2000-KR1255 W 20001103

AB The present invention provides hydrophobic heparin conjugates which are sol. not in water but in org. solvents, a prep. method and a use thereof. Particularly, the present invention provides the hydrophobic heparin conjugates which are prep'd. by covalently binding polymer and hydrophobic materials to heparin. The hydrophobic heparin conjugates of the present invention maintain a good antithrombogenic effect and are insol. in water by their hydrophobicity, so they can be effectively used for coating agents to modify the surface of medical devices. For example, a hydrophobic multicomponent heparin conjugates were synthesized from heparin, polyacrylic acid and octadecylamine in a molar ratio of 1:5:100. The surface of angiocatheter made of polyurethane and glass were coated with the conjugate by a dipping method and dried. The heparin/polyacrylic acid/octadecylamine conjugate showed great adhesiveness to the materials and had no peeling phenomena by swelling in aq. soln. The hydrophobic multicomponent heparin conjugates were adhered to the material with stability while maintaining the unique characteristics of heparin and antithrombotic activity.

IT 9002-89-5DP, Polyvinyl alcohol, conjugates with heparin
9004-61-9DP, Hyaluronic acid, conjugates with heparin
9005-49-6DP, Heparin, conjugates with macromols.
9012-76-4DP, Chitosan, conjugates with heparin
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydrophobic multicomponent heparin conjugates for
antithrombogenic coatings for prosthetics and medical goods)

RN 9002-89-5 HCPLUS
CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

$$\text{H}_2\text{C}=\text{CH}-\text{OH}$$

RN 9004-61-9 HCPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9005-49-6 HCPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9012-76-4 HCPLUS
CN Chitosan (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 3 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:713823 HCPLUS
DOCUMENT NUMBER: 135:262268
TITLE: Pharmaceutical dosage form for oral administration of hydrophilic drugs, particularly low molecular weight heparin
INVENTOR(S): Chen, Feng-Jing; Patel, Mahesh V.; Fikstad, David T.
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S.
 Ser. No. 375,636.
 CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

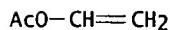
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001024658	A1	20010927	US 2000-751968	20001229 <--
US 6458383	B2	20021001		
US 6309663	B1	20011030	US 1999-375636	19990817 <--
WO 2001012155	A1	20010222	WO 2000-US18807	20000710 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002032171	A1	20020314	US 2001-877541	20010608 <--
WO 2002053100	A2	20020711	WO 2001-US50752	20011228 <--
WO 2002053100	A3	20030327		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			US 1999-375636 A2 19990817	
			WO 2000-US18807 A 20000710	
			US 1999-345615 A2 19990630	
			US 2000-751968 A2 20001229	

AB A delayed release pharmaceutical dosage form for oral administration of a hydrophilic drug, e.g., a polysaccharide drug such as low mol. wt. heparin, are provided. The dosage form comprises a compn. of: (a) a therapeutically effective amt. of low mol. wt. heparin; (b) a bile salt or bile acid; (c) at least one surfactant selected from hydrophilic surfactants, lipophilic surfactants, and mixts. thereof; and a means for delaying release of the compn. from the dosage form following oral administration. Osmotic drug delivery systems for oral administration of a hydrophilic drug are also provided, wherein an osmotically activated device houses the drug, a bile salt or bile acid, and at least one surfactant selected from the group consisting of hydrophilic surfactants, lipophilic surfactants, and mixts. thereof. Methods for administering hydrophilic drugs, particularly polysaccharide drugs such as low mol. wt. heparin, are also provided. Capsules contg. Enoxaparin sodium (a LMW heparin) 50, deoxycholic acid sodium salt 100, Incrocas 35 300, and Capryol 90 300 mg were prep'd. The capsules were dipped briefly in a soln. of cellulose acetate phthalate 11, triacetin 2.2% in acetone and dried in air at room temp. The capsule were dipped and dried repeatedly until a coating wt. of .1toreq.10% (dissoln. pH range of about 5.5-6.5 was achieved).

IT 9003-20-7, Polyvinyl acetate 9003-39-8, Polyvinyl pyrrolidone 9004-61-9, Hyaluronic acid 9005-49-6, Heparin, biological studies 9041-08-1, Enoxaparin sodium 24937-78-8, Ethylene-vinyl acetate copolymer 25609-89-6, Vinylacetate crotonic acid copolymer
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmaceutical dosage form for oral administration of hydrophilic

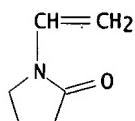
drugs, particularly low mol. wt. heparin)
 RN 9003-20-7 HCPLUS
 CN Acetic acid ethenyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
CMF C4 H6 O2

RN 9003-39-8 HCPLUS
 CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O

RN 9004-61-9 HCPLUS
 CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

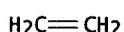
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 RN 9041-08-1 HCPLUS
 CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 RN 24937-78-8 HCPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

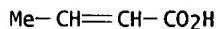
CRN 108-05-4
CMF C4 H6 O2

CM 2

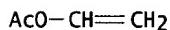
CRN 74-85-1
CMF C2 H4

RN 25609-89-6 HCPLUS
 CN 2-Butenoic acid, polymer with ethenyl acetate (9CI) (CA INDEX NAME)

CM 1

CRN 3724-65-0
CMF C4 H6 O2

CM 2

CRN 108-05-4
CMF C4 H6 O2

L47 ANSWER 4 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:460978 HCPLUS
 DOCUMENT NUMBER: 133:355165
 TITLE: Polymeric systems based on derivatives of ethylene-vinyl alcohol copolymers
 AUTHOR(S): Marconi, W.; Cordelli, S.; Napoli, A.; Piozzi, A.
 CORPORATE SOURCE: Department of Chemistry, University of Rome "La Sapienza", Rome, 00185, Italy
 SOURCE: Journal of Bioactive and Compatible Polymers (2000), 15(3), 257-271
 CODEN: JBCPEV; ISSN: 0883-9115
 PUBLISHER: Technomic Publishing Co., Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB To obtain polymers with improved hemocompatibility properties, com. ethylene-vinyl alc. copolymers (EVAL) were chem. modified, by the introduction of stearoyl groups to bind albumin and quaternary ammonium groups to bind heparin. These novel polymer composites were characterized by FT-IR and 1H-NMR spectroscopy. The amt. of heparin and albumin bonded by these polymers were detd. and the influence of the adsorption sequence (heparin+albumin or vice versa) was evaluated. The amt. of adsorbed albumin was proportional to the stearoyl content of the polymer. When heparin was exposed to polymer surfaces contg. quaternary ammonium groups, the amt. of bonded heparin was proportional to the content of pos. charged groups. An in vitro evaluation of the anti-clotting properties and of the adhesion characteristics of the polymer surfaces contg. both stearoyl groups and quaternary ammonium groups exhibited, after heparinization, good anticoagulant activity. This activity was retained after the albuminization. Platelet adhesion tests showed that albuminization of polymer films contg. only stearoyl residues improved their behavior towards platelet adhesion.

IT 9005-49-6DP, Heparin, reaction products with activated EVAL, biological studies 25067-34-9DP, Eval, heparinized or albuminized
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(biocompatible polymeric systems based on derivs. of ethylene -vinyl alc. copolymers)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25067-34-9 HCPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

CM 2

CRN 74-85-1
CMF C2 H4

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 5 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:182122 HCPLUS
 DOCUMENT NUMBER: 133:22375
 TITLE: Multi-layered thromboresistant thin films on poly(vinylchloride) (PVC) surfaces; a spectroscopic study
 AUTHOR(S): Kim, Huang; Urban, Marek W.
 CORPORATE SOURCE: School of Polymers and High Performance Materials, The University of Southern Mississippi, Hattiesburg, MS, 39406, USA
 SOURCE: Polymeric Materials Science and Engineering (2000), 82, 392-393
 CODEN: PMSEDG; ISSN: 0743-0515
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The formation of multi-layered structures that consist of polyethyleneimine, dextran sulfate and heparin sulfate attached to PVC surfaces is reported. ATR FT-IR spectra of the polymers were detd.
 IT 272442-93-0P
 RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (spectroscopic study of multi-layered thromboresistant thin films on PVC surfaces)
 RN 272442-93-0 HCPLUS
 CN Heparin, compd. with aziridine graft polymer with chloroethene (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 272442-92-9
CMF (C2 H5 N . C2 H3 Cl)x
CCI PMS

CM 3

CRN 151-56-4
CMF C2 H5 N

H
A

CM 4

CRN 75-01-4
CMF C2 H3 C1

$\text{H}_2\text{C}=\text{CH}-\text{C}_1$

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 6 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:144524 HCPLUS
 DOCUMENT NUMBER: 132:185484
 TITLE: Thromboresistant coating of medical devices using silanes or siloxanes
 INVENTOR(S): Shah, Chirag B.; Tedeschi, Gene; Wolfgang, Laurel L.
 PATENT ASSIGNEE(S): Medtronic Ave, Inc., USA
 SOURCE: Eur. Pat. Appl., 24 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 982041	A1	20000301	EP 1999-116428	19990820 <-- R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
US 2001034336	A1	20011025	US 2001-862710	20010523 <--

PRIORITY APPLN. INFO.: US 1998-138464 A 19980821
 AB Coatings are provided in which biopolymers may be covalently linked to a substrate. Such biopolymers include those that impart thromboresistance and/or biocompatibility to the substrate, which may be a medical device. Coatings disclosed include those that permit coating of a medical device in a single layer, including coatings that permit applying the single layer without a primer. Suitable biopolymers include heparin complexes, and linkage may be provided by a silane having isocyanate functionality. Plasma deposition and solvent swelling techniques are described as preferred methods of depositing a derivatized silane or a silane-heparin coating. Stainless steel stents were coated with a formulation of 1% heparin-tridodecylmethylammonium chloride complex, 2% silane and 97% THF. The stents were dipped once in the formulation, with a dwell time of 5 s at a coating speed of 10 in/min to give a single layer of coating. The coating showed heparin activity after 1 wk of exposure to saline.

IT 259665-61-7
 RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (thromboresistant coating of medical devices using silanes or siloxanes)

RN 259665-61-7 HCPLUS
 CN Heparin, compd. with 1-ethenyl-2-pyrrolidinone homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

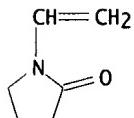
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 9003-39-8
 CMF (C₆ H₉ N O)x
 CCI PMS

CM 3

CRN 88-12-0
 CMF C₆ H₉ N O



L47 ANSWER 7 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:98671 HCPLUS
 DOCUMENT NUMBER: 132:156879
 TITLE: Physiologically compatible ion complex, coating material for medical goods and coating method using it
 INVENTOR(S): Yoshioka, Hiroshi; Mori, Yuichi; Kubota, Sunao
 PATENT ASSIGNEE(S): M & M Laboratory Co., Ltd., Japan; Terumo Kabushiki Kaisha
 SOURCE: PCT Int. Appl., 43 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006651	A1	20000210	WO 1999-JP4021	19990727 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9949283	A1	20000221	AU 1999-49283	19990727 <--
EP 1020495	A1	20000719	EP 1999-933116	19990727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6555225	B1	20030429	US 2000-535532	20000327
PRIORITY APPLN. INFO.:			JP 1998-211008 A	19980727
			WO 1999-JP4021 W	19990727

AB The ion complex is insol. in water and sol. in water-contg. org. solvents and comprises a water-insol. polyion and a water-sol. polyion preferably from physiol. active compd. having blood anticoagulant (e.g., heparin) or

antibacterial activity. The ion complex is useful as coating for use on medical goods, e.g., surgical tubes, for reducing health complication. Thus, dissolving diacetone acrylamide 2.0, Blemmer PME 4000 (PEG monomethacrylate) 0.14, a 75% aq. soln. of N,N-dimethylaminopropylacrylamide Me chloride quaternary ammonium salt 0.19 and Na heparin 0.14 g in water 7.5 g, mixing with 6 g EtOH, 0.2 mL a 10% ammonium persulfate aq. soln. and 20 .mu.L N,N,N',N'-tetramethylethylenediamine at room temp. for 2 h, evapg., washing and freeze drying gave an ion complex which was insol. in water and sol. in aq. EtOH. A viscous coating was obtained by mixing 0.2 g the complex in 2.3 g an aq. EtOH (18% water content).

IT 257877-23-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(physiol. compatible ion complex, coating material for medical goods and coating method)

RN 257877-23-9 HCPLUS

CN D-Streptamine, O-3-amino-3-deoxy-.alpha.-D-glucopyranosyl-(1.fwdarw.6)-O-[2,6-diamino-2,3,4,6-tetra(deoxy-.alpha.-D-erythro-hexopyranosyl-(1.fwdarw.4))-2-deoxy-, sulfate (salt), compd. with N-(1,1-dimethyl-3-oxobutyl)-2-propenamide polymer with ethyl 2-propenoate and sodium ethenylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 257877-22-8

CMF (C9 H15 N 02 . C8 H8 O3 S . C5 H8 O2 . Na)x

CCI PMS

CM 2

CRN 27457-28-9

CMF C8 H8 O3 S . Na

CCI IDS

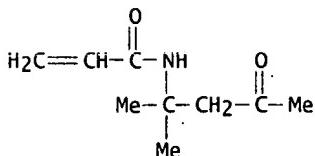
D1-CH=CH₂D1-SO₃H

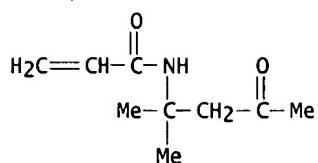
● Na

CM 3

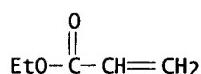
CRN 2873-97-4

CMF C9 H15 N 02





CM 4

CRN 140-88-5
CMF C5 H8 O2

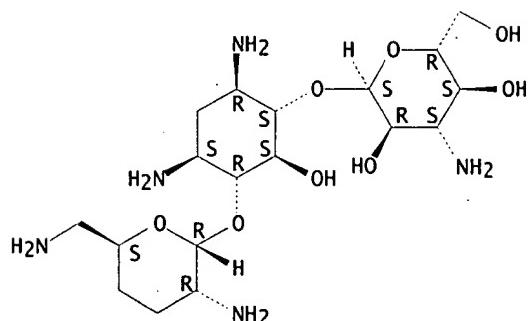
CM 5

CRN 58580-55-5
CMF C18 H37 N5 O8 . x H2 O4 S

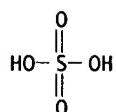
CM 6

CRN 34493-98-6
CMF C18 H37 N5 O8

Absolute stereochemistry.



CM 7

CRN 7664-93-9
CMF H2 O4 S

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:764076 HCPLUS
 DOCUMENT NUMBER: 132:26813
 TITLE: Preparation and anticoagulant activity of amphiphilic heparin conjugates
 INVENTOR(S): Byun, Youngro; Lee, Yong Kyu
 PATENT ASSIGNEE(S): Mediplex Corporation, Korea, S. Korea
 SOURCE: PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9961481	A1	19991202	WO 1999-KR242	19990514 <--
W: AE, AT, AU, BR, CA, CH, CN, DE, DK, ES, FI, GB, HU, ID, IN, JP, KP, KZ, MN, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, TR, UA, ZA				
US 6245753	B1	20010612	US 1999-300173	19990427 <--
AU 9937358	A1	19991213	AU 1999-37358	19990514 <--
GB 2342357	A1	20000412	GB 1917-94	19990514 <--
DE 19981169	T	20001116	DE 1999-19981169	19990514 <--
GB 2342357	B2	20020327	GB 2000-1794	19990514 <--
JP 2002516355	T2	20020604	JP 2000-550884	19990514 <--
US 2002013292	A1	20020131	US 2001-852131	20010509 <--
US 6589943	B2	20030708		
WO 2002089820	A1	20021114	WO 2001-KR1722	20011012 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			KR 1998-19469	A 19980528
			KR 1999-14003	A 19990420
			US 1999-300173	A 19990427
			WO 1999-KR242	W 19990514
			US 2001-852131	A 20010509

- AB Amphiphilic heparin derivs. were synthesized by conjugation to bile acids, sterols, and alkanoic acids. The hydrophobicity of the heparin derivs. depended on the feed mole ratio of heparin to hydrophobic agent. The heparin derivs. were slightly hydrophobic and exhibited good solv. in a water-acetone solvent, as well as water. The heparin derivs. have a high anticoagulant activity. These slightly hydrophobic heparin derivs. can be absorbed in the gastric intestinal tract and can be used as oral dosage form. Also, the heparin derivs. can be used for surface modification to prevent coagulation on medical devices such as extracorporeal devices and implanted devices.
- IT 24937-78-8, Ethylene-vinyl acetate copolymer
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (carrier; prepn. and anticoagulant activity of amphiphilic heparin conjugates)
- RN 24937-78-8 HCPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
 CMF C4 H6 O2AcO-CH=CH₂

CM 2

CRN 74-85-1
CMF C2 H4

IT 9005-49-6P, Heparin, biological studies
 9041-08-1P, Heparin sodium
 RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (conjugate; prepn. and anticoagulant activity of amphiphilic heparin conjugates).
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 RN 9041-08-1 HCPLUS
 CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 9 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1999:352563 HCPLUS
 DOCUMENT NUMBER: 131:134577
 TITLE: Characterization of transient platelet contacts on a polyvinyl alcohol hydrogel by video microscopy
 AUTHOR(S): Godo, Matthew N.; Sefton, Michael V.
 CORPORATE SOURCE: Department of Chemical Engineering and Applied Chemistry and Centre for Biomaterials, University of Toronto, Toronto, ON, M5S 3E5, Can.
 SOURCE: Biomaterials (1999), 20(12), 1117-1126
 CODEN: BIMADU; ISSN: 0142-9612
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Acridine orange labeled, washed human platelets were counted and tracked on polyvinyl alc. (PVA), heparin-PVA and polyethylene (PE)-coated coverslips with a view to understand why transient contact on the PVA hydrogels lead to elevated platelet activation and consumption relative to polyethylene. Over the 4 min of initial contact that was studied, platelet adhesion was higher on PE than on PVA or heparin-PVA at both 40 and 200 s-1, as expected, regardless of whether the surfaces were pre-treated with albumin or fibrinogen. Not all platelets appearing to make contact with the surface, actually attached. For example, less than 2% of the platelets contacting albumin pre-treated PVA (at 40 s-1) remained adherent at the end of the initial 60 s observation time, while the corresponding no. for PE was greater than 9%. A greater fraction of the platelets remained adherent at the higher shear rate or with fibrinogen pre-treatment, but the difference between PVA and PE remained similar: for example, with fibrinogen pre-treatment at 200 s-1, apprx.25% of the platelet contacts resulted in adhesion on PVA while 66% did so on PE. While net platelet adhesion was less for the hydrogels, than for PE, the total no. of contacts (adherents + non-adherents) were more comparable and unexpectedly higher for albumin pre-treatment than for fibrinogen. Net platelet adhesion is but one component of the total platelet interaction with a material surface. Fluorescent video microscopy has been shown to be a useful, albeit not unequivocal, method for assessing the platelets that make contact with but do not adhere to a surface.

IT 9002-89-5, Polyvinyl alcohol
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (characterization of transient platelet contacts on a polyvinyl alc.
 hydrogel by video microscopy)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O



IT 9005-49-6, Heparin, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (coating with poly(vinyl alc.) and; characterization of transient platelet contacts on a polyvinyl alc. hydrogel by video microscopy)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 10 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:150594 HCPLUS

DOCUMENT NUMBER: 126:255386

TITLE: Development of chitosan/polyethylene
 vinyl acetate co-matrix: controlled release of aspirin-heparin for preventing cardiovascular thrombosis

AUTHOR(S): Vasudev, Sindhu C.; Chandy, Thomas; Sharma, Chandra P.
 CORPORATE SOURCE: Div. Biosurface Technology, Sree Chitra Tirunal Inst.

SOURCE: Med. Sci. Technology, Trivandrum, 695 012, India
 Biomaterials (1997), 18(5), 375-381

PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Aspirin and heparin were embedded in chitosan/polyethylene vinyl acetate co-matrix to develop a prolonged release form. The in vitro release profiles of these drugs from the co-matrix system were monitored in Tris HCl buffer pH 7.4, using a UV spectrophotometer. The amt. of drug release was initially much higher, followed by a const. slow release profile for a prolonged period. The initial burst release was substantially modified with styrene-butadiene coatings. From SEM studies it appears that the drugs diffuse out slowly to the dissoln. medium through the micropores of the co-matrix. The released aspirin-heparin from the co-matrix system had shown their antiplatelet and anticoagulant functions. The results propose the possibility of delivering drug combinations, having synergistic effects for therapeutic applications.

IT 9005-49-6, Heparin, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(chitosan/polyethylene vinyl acetate co-matrix for controlled release of aspirin-heparin for preventing cardiovascular thrombosis)

RN 9005-49-6 HCPLUS

← Main mic.
 R857.M3 B568

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9012-76-4, Chitosan 24937-78-8, Ethylene-vinyl acetate copolymer

RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (chitosan/polyethylene vinyl acetate co-matrix for controlled release of aspirin-heparin for preventing cardiovascular thrombosis)

RN 9012-76-4 HCPLUS

CN Chitosan (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1

CMF C2 H4

H₂C=CH₂

L47 ANSWER 11 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1996:126741 HCPLUS

DOCUMENT NUMBER: 124:156148

TITLE: Artificial blood vessel and process for producing it

INVENTOR(S): Matsuda, Takehisa; Nakajima, Nobuyuki; Kito, Hiroyuki

PATENT ASSIGNEE(S): Seikagaku Kogyo K. K., Japan

SOURCE: Can. Pat. Appl., 27 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2132033	AA	19950916	CA 1994-2132033	19940914 <-
JP 07250887	A2	19951003	JP 1994-68927	19940315 <-

PRIORITY APPLN. INFO.: JP 1994-68927 19940315

AB This invention provides a more functionalized artificial blood vessel which can be organized by independently designing its inner and outer surfaces and endowing them with resp. different biocompatibilities, as well as a process for producing the same. The artificial blood vessel comprises a tubular support having a layer of photogelled cinnamic acid-bound chondroitin sulfate (C-CS) coated on the inner surface thereof and a layer of photogelled coumarin-bound gelatin (C-GT) coated on the outer surface thereof. The process for producing the above artificial blood vessel comprises coating a layer of coumarin-bound gelatin on the outer surface of a tubular support and a layer of cinnamic acid-bound chondroitin sulfate on the inner surface of the support and irradiating

each of the layers with light. An artificial blood vessel made of Dacron was used as a support, which was soaked in a C-GT aq. soln. and irradiated with UV light (λ . >310 nm). A C-CS aq. soln. was injected into the resulting support and internally irradiated with UV light (λ . >270 nm). The obtained blood vessel was transplanted in a dog and its biocompatibility was tested.

IT 9007-28-7DP, Chondroitin sulfate, reaction product with cinnamic acid chloride
 RL: SPN (Synthetic preparation); TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation);
 USES (Uses)
 (manuf. of artificial blood vessel with inner coating of cinnamate-bound chondroitin sulfate and outer coating of coumarin-bound gelatins)

RN 9007-28-7 HCPLUS

CN Chondroitin, hydrogen sulfate (9CI) (CA INDEX NAME)

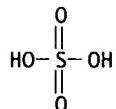
CM 1

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



L47 ANSWER 12 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:307368 HCPLUS

DOCUMENT NUMBER: 122:89343

TITLE: Study of hemodialysis materials: physicochemical and biological characterization of EVALVA, EVAPA, and heparinized EVAPA

AUTHOR(S): Barbucci, R.; Albanese, A.; Tempesti, F.; Baszkin, A.; Eloy, R.; Weill, N.; Martuscelli, E.; Cimmino, S.

CORPORATE SOURCE: CRISMA, Universita di Siena, Siena, 53100, Italy

SOURCE: Journal of Materials Science: Materials in Medicine (1994), 5(12), 844-9

CODEN: JSMMEL; ISSN: 0957-4530

PUBLISHER: Chapman & Hall

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Partially hydrolyzed ethylene/vinyl acetate copolymers were modified by the covalent binding of a heparin-complexing polymer and further heparinized in order to improve their blood compatibility. These heparinizable polymeric materials (EVAPA) were obtained by a 2-step reaction between an ethylene/vinyl alc./vinyl acetate (EVALVA) terpolymer, and the heparin complexing polymer N2LL. The physicochemical characterization of EVALVA, EVAPA and heparinized-EVAPA was carried out through thermal anal., SEM, contact angle, potentiometric measurements, water uptake and FT-IR spectroscopic measurements. The biocompatibility of the above-mentioned samples was evaluated using in vitro methods, through the detn. of heparin release in phosphate buffer soln. and in human plasma, and with the investigation of hemostasis activation.

IT 9005-49-6D, Heparin, reaction products with polyamide-polyamines and ethylene-vinyl alc.-vinyl acetate copolymer 24937-78-8D, Ethylene-vinyl acetate copolymer, hydrolyzed, reaction products with polyamide-polyamines
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (physicochem. and biol. characterization of heparinized hemodialysis polymers)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
 CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1
 CMF C2 H4

H₂C=CH₂

L47 ANSWER 13 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1995:307367 HCPLUS
 DOCUMENT NUMBER: 122:89342
 TITLE: In situ ATR/FTIR studies of protein adsorption on polymeric materials: effectiveness of surface heparinization
 AUTHOR(S): Magnani, A.; Busi, E.; Barbucci, R.
 CORPORATE SOURCE: CRISMA, Universita di Siena, Siena, 53100, Italy
 SOURCE: Journal of Materials Science: Materials in Medicine (1994), 5(12), 839-43
 CODEN: JSMMEL; ISSN: 0957-4530
 PUBLISHER: Chapman & Hall
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The adsorption of 2 proteins from human plasma (human serum albumin and human fibrinogen onto 6 different polymeric surfaces, 2 of which are heparinized), was studied by in situ ATR/FTIR spectroscopy. The different surface characteristics are reflected by different interfacial behaviors of the 2 proteins, but while both proteins unfold upon adsorption on all the different non-heparinized materials, they maintain the native conformation once adsorbed on the heparinized surfaces. These findings emphasize the effectiveness of surface heparinization.

IT 9005-49-6D, Heparin, reaction products with polyamide-polyamines 24937-78-8D, Ethylene-vinyl acetate copolymer, hydrolyzed, reaction products with polyamide-polyamines and heparin
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (ATR/FTIR studies of protein adsorption on heparinized polymers)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

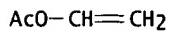
RN 24937-78-8 HCPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

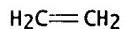
CMF C4 H6 O2



CM 2

CRN 74-85-1

CMF C2 H4



L47 ANSWER 14 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:663548 HCPLUS

DOCUMENT NUMBER: 121:263548

TITLE: Heparin surface immobilization through hydrophilic
spacers: thrombin and antithrombin III binding
kinetics

AUTHOR(S): Byun, Youngro; Jacobs, Harvey A.; Kim, Sung Wan

CORPORATE SOURCE: Dep. Pharmaceutics Pharmaceutical Chemistry, Univ.
Utah, Salt Lake City, UT, 84108, USA

SOURCE: Journal of Biomaterials Science, Polymer Edition (1994), 6(1), 1-13

CODEN: JBSEEA; ISSN: 0920-5063

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The immobilization of heparin onto polymer surfaces using hydrophilic spacer groups has been effective in curtailing surface induced thrombus formation. In this study, the effect of hydrophilic spacers (PEO) on the binding kinetics of immobilized heparin with antithrombin III (ATIII) and thrombin was investigated. Monodispersed, low-mol. wt. heparin was fractionated on an ATIII affinity column to isolate high-ATIII affinity heparin. This high-ATIII affinity fraction was immobilized onto a styrene/p-aminostyrene random copolymer surface using hydrophilic polyethylene oxide (PEO) spacer groups. Styrene/p-aminostyrene random copolymer was chosen as the model surface to provide quant. and reproducible surface concns. of available amine groups, grafted PEO spacers, and immobilized heparin. The polymer substrate was coated onto glass beads, tolylene diisocyanate-modified PEO was covalently coupled to the surface, followed by heparin immobilization. The bioactivity of immobilized heparin was 16.2%, relative to free heparin, and a 1:1 binding ratio between heparin and PEO was achieved. The binding of ATIII and thrombin to control surfaces (no heparin), sol. heparin, heparin immobilized directly onto the surface, and heparin immobilized via spacer groups, were compared. Sol. heparin bound both thrombin and ATIII, while heparin immobilized directly onto the surface bound only thrombin. Spacer-immobilized heparin bound both ATIII and thrombin, although to a lesser extent than sol. heparin. Thus, the enhanced bioactivity of spacer-immobilized heparin, compared to direct-immobilization, may be attributed to the retention of ATIII binding.

IT 158747-37-6P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(thrombin and antithrombin III binding to polymer-immobilized heparin surfaces)

RN 158747-37-6 HCPLUS

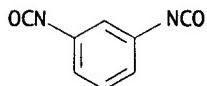
CN Heparin, polymer with 1,3-diisocyanatomethylbenzene, 4-ethenylbenzenamine, ethenylbenzene and .alpha.-hydro-.omega.-hydroxypoly(oxy-1,2-ethanediyl), graft (9CI) (CA INDEX NAME)

CM 1

CRN 26471-62-5

CMF C9 H6 N2 O2

CCI IDS



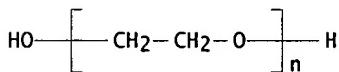
D1-Me

CM 2

CRN 25322-68-3

CMF (C2 H4 O)n H2 O

CCI PMS



CM 3

CRN 9005-49-6

CMF Unspecified

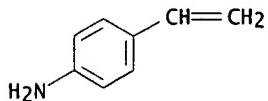
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 1520-21-4

CMF C8 H9 N



CM 5

CRN 100-42-5

CMF C8 H8

H₂C=CH-Ph

L47 ANSWER 15 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1994:517492 HCPLUS
 DOCUMENT NUMBER: 121:117492
 TITLE: Heparin release from polymer complex
 AUTHOR(S): Kwon, Ick Chan; Bae, You Han; Kim, Sung Wan
 CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical
 Chemistry and Center for Controlled Chemical Delivery,
 University of Utah, 421 Wakaraway No. 318, Salt Lake
 City, UT, 84108, USA
 SOURCE: Journal of Controlled Release (1994), 30(2),
 155-9
 CODEN: JCREEC; ISSN: 0168-3659
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB An electro-erodible polyelectrolyte complex was prep'd. and investigated
 for a pulsatile drug release system. An insol. polyelectrolyte complex
 was formed by combining two water-sol. polymers, poly(allylamine) and
 heparin. Upon the application of an elec. current, a rapid structural
 change of the complex occurred, dissolving the polymer matrix in
 proportion to the intensity of an applied elec. current. The disruption
 of ionic bonds in the polymer matrix attached to the cathode and
 subsequent release of heparin was due to the locally increased pH near the
 cathode (resulting from hydroxyl ion prodn.). Thus, the release pattern
 of a model bioactive macromol., heparin, followed the applied elec.
 current, primarily due to surface erosion of the polymer matrix.
 IT 155655-56-4
 RL: BIOL (Biological study)
 (heparin release from, elec. current stimulated)
 RN 155655-56-4 HCPLUS
 CN Heparin, compd. with 2-propen-1-amine homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

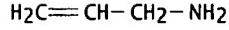
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 30551-89-4
 CMF (C3 H7 N)x
 CCI PMS

CM 3

CRN 107-11-9
 CMF C3 H7 N



L47 ANSWER 16 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1994:330933 HCPLUS
 DOCUMENT NUMBER: 120:330933
 TITLE: Pulsatile drug release by electric stimulus
 AUTHOR(S): Bae, You Han; Kwon, Ick Chan; Kim, Sung Wan
 CORPORATE SOURCE: Cent. Controlled Chem. Delivery, Univ. Utah, Salt Lake
 City, UT, 84112, USA
 SOURCE: ACS Symposium Series (1994), 545(Polymeric
 Drugs and Drug Administration), 98-110
 CODEN: ACSMC8; ISSN: 0097-6156

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Elec. currents were applied to polymeric monolithic devices to produce pulsatile drug release. The polymeric matrixes used were either elec. charged networks, or polymer-polymer complexes based on hydrogen bonding or electrostatic interactions. Pos. charged drug was released in an on-off manner from a neg. charged network. The ionically bound drug was freed from the polymer chains by ion-exchange with H+ ions. The polymer-polymer interactions in the formed complexes were perturbed by ionization or deionization of one part of the polymer pairs by either increasing or decreasing pH around electrodes. This resulted in polymer surface erosion and pulsatile release of the drugs entrapped in the matrixes.

IT 155655-56-4P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, for elec. stimulus-induced drug release)

RN 155655-56-4 HCPLUS

CN Heparin, compd. with 2-propen-1-amine homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

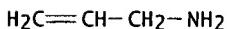
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 30551-89-4
 CMF (C3 H7 N)x
 CCI PMS

CM 3

CRN 107-11-9
 CMF C3 H7 N



L47 ANSWER 17 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1994:307560 HCPLUS
 DOCUMENT NUMBER: 120:307560
 TITLE: Medical goods coated with oligosaccharides or polysaccharides
 INVENTOR(S): Uchama, Hideki; Watanabe, Junichiro
 PATENT ASSIGNEE(S): Terumo Corp, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06086808	A2	19940329	JP 1992-238606	19920907 <-
PRIORITY APPLN. INFO.:			JP 1992-238606	19920907

AB Oligosaccharides or polysaccharides such as heparin are reduced in the presence of ammonium salts, forming amino groups at the carbohydrate terminals, and bound to functional groups of substrates via amino groups. The biol. activity of the oligosaccharides or polysaccharides are not decreased after binding to the substrates. For example, an

antithrombogenic poly(vinyl chloride) tube on which heparin had been immobilized was prepd.

IT 9005-49-6, Heparin, biological studies
 RL: BIOL (Biological study)
 (immobilization of, on polymer in antithrombogenic medical goods manuf.)
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-86-2, Poly(vinyl chloride)
 RL: BIOL (Biological study)
 (tubes, heparin immobilization on, in antithrombogenic medical goods manuf.)
 RN 9002-86-2 HCPLUS
 CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4
 CMF C2 H3 C1

H2C=CH-C1

L47 ANSWER 18 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:280360 HCPLUS
 DOCUMENT NUMBER: 120:280360
 TITLE: Manufacture of prosthetic materials
 INVENTOR(S): Inai, Koji; Nakaji, Shuhei; Akasu, Hiroyuki
 PATENT ASSIGNEE(S): Kuraray Co, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06063121	A2	19940308	JP 1992-224452	19920824 <-
JP 2974854	B2	19991110		

PRIORITY APPLN. INFO.: JP 1992-224452 19920824

AB An org. polymer substrate is bound to a silane crosslinking agent, a spacer, and biol. active agent, in that order to give a prosthetic material. For example, an antithrombogenic sheet was prepd. by treating a polymethylpentene sheet with 3-glycidoxypropylmethoxysilane crosslinking agent, followed by polyethyleneimine (a spacer) and aldehyde-modified heparin (an antithrombotic agent). Heparin is securely bound to the sheet for a long period while the sheet was in contact with blood plasma.

IT 9002-86-2D, Poly(vinyl chloride), reaction products with silane derivs., aldehyde-modified heparin bound, via spacer 25067-34-9D, Ethylene-vinyl alcohol copolymer, reaction products with silane derivs., heparin bound, via spacer
 RL: BIOL (Biological study)
 (antithrombogenic medical goods manuf. with)

RN 9002-86-2 HCPLUS
 CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4
 CMF C2 H3 C1

H2C=CH-C1

RN 25067-34-9 HCPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

H2C=CH-OH

CM 2

CRN 74-85-1
 CMF C2 H4

H2C=CH2

IT 9005-49-6, Heparin, uses
 RL: USES (Uses)
 (immobilization of, on crosslinked polymers, for antithrombogenic medical goods manuf.)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

**** STRUCTURE DIAGRAM IS NOT AVAILABLE ****

L47 ANSWER 19 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1994:226845 HCPLUS
 DOCUMENT NUMBER: 120:226845
 TITLE: Heparin-containing block copolymers. Part II. In vitro and ex vivo blood compatibility
 AUTHOR(S): Vulic, I.; Okano, T.; Van Der Gaag, F. J.; Kim, S. W.; Feijen, J.
 CORPORATE SOURCE: Dep. Chem. Technol., Univ. Twente, Enschede, 7500 AE, Neth.
 SOURCE: Journal of Materials Science: Materials in Medicine (1993), 4(5), 448-59
 CODEN: JSMMEL; ISSN: 0957-4530
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Newly synthesized heparin-contg. block copolymers, consisting of a hydrophobic block of polystyrene (PS), a hydrophilic spacer-block of poly (ethylene oxide) (PEO) and covalently bonded heparin (Hep) as bioactive block, were coated either onto glass, polydimethyl siloxane, polyurethane or PS substrates. Coated surfaces were characterized by detn. of the surface-bound heparin activity, adsorption of AT III, plasma recalcification time assays, adhesion of platelets and by an ex vivo rabbit A-A shunt model. Heparin was available at the surface of all heparin-bound surfaces to interact with AT III and thrombin and to prevent the formation of clots. The max. immobilized heparin activity was 5.5 times 10⁻³ U cm⁻². Coated surfaces showed a significant prolongation of the plasma recalcification times as compared to control surfaces, due to surface-immobilized heparin. The platelet adhesion demonstrated that platelets reacted only minimally with the heparin-contg. block copolymers in the test system and that the heparin-contg. block copolymers seemed to passify the surface as compared to control surfaces. In the ex vivo A-A

shunt expts., which were carried out under low flow and low shear conditions, the heparin-contg. block copolymers exhibited prolonged occlusion times, indicating the ability of the heparin-contg. block copolymers to reduce thrombus formation at the surface.

IT 114954-84-6

RL: BIOL (Biological study)
(blood compatibility and properties of substrate-coated)

RN 114954-84-6 HCPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
CMF C8 H8



CM 3

CRN 75-21-8
CMF C2 H4 O

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L47 ANSWER 20 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1994:137558 HCPLUS
 DOCUMENT NUMBER: 120:137558
 TITLE: Photocurable glycosaminoglycan derivatives,
 crosslinked glycosaminoglycans and method of
 production thereof
 INVENTOR(S): Matsuda, Takehisa; Moghaddan, Minoo J.; Sakurai,
 Katsukiyo
 PATENT ASSIGNEE(S): Seikagaku Kogyo K. K., Japan
 SOURCE: Eur. Pat. Appl., 55 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 554898	A2	19930811	EP 1993-101838	19930205 <--
EP 554898	A3	19940126		
EP 554898	B1	19970507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 06073102	A2	19940315	JP 1992-355441	19921221 <--
JP 2855307	B2	19990210		
RU 2139886	C1	19991020	RU 1993-4491	19930203 <--
CA 2088831	AA	19930806	CA 1993-2088831	19930204 <--

HU 71625	A2	19960129	HU 1993-297	19930204 <--
HU 215503	B	19990128	AU 1993-32878	19930205 <--
AU 9332878	A1	19930812	CN 1993-102682	19930205 <--
AU 670921	B2	19960808	US 1993-13799	19930205 <--
CN 1075970	A	19930908	AT 1993-101838	19930205 <--
CN 1083455	B	20020424	ES 1993-101838	19930205 <--
US 5462976	A	19951031	US 1995-476236	19950607 <--
AT 152736	E	19970515	JP 1992-47744	A 19920205
ES 2102537	T3	19970801	JP 1992-203209	A 19920708
US 5763504	A	19980609	JP 1992-355441	A 19921221
PRIORITY APPLN. INFO.:			US 1993-13799	B3 19930205

AB The title biopolymers with good physiol. compatibility and biol. degradability, useful for medical (e.g., prosthetic moldings) or pharmaceutical use (e.g., for drug slow-release coating), are prep'd. based on modification of functional groups of substrates via, e.g., ester and amide linkages, using photosensitive modifiers which can be cured by free-radical mechanism. Example of a title deriv. was the cinnamate ester of hyaluronic acid which was formed by using cinnamoyl chloride in esterification; and the DMF soln.-cast film of the ester could be cured by UV light.

IT 152787-17-2

RL: USES (Uses)
(photoprepn. of crosslinked biodegradable biocompatible, for medical use)

RN 152787-17-2 HCPLUS

CN Chondroitin, hydrogen sulfate 3-phenyl-2-propenoate, homopolymer (9CI)
(CA INDEX NAME)

CM 1

CRN 152787-16-1
CMF C9 H8 O2 . x H2 O4 S . x Unspecified

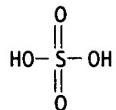
CM 2

CRN 9007-27-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 7664-93-9
CMF H2 O4 S



CM 4

CRN 621-82-9
CMF C9 H8 O2

Ph-CH=CH-CO₂H

IT 153147-07-0P

RL: PRP (Properties); PREP (Preparation)
 (prepn. and properties of, photocurable, biodegradable and compatible,
 for pharmaceutical and medical use)

RN 153147-07-0 HCPLUS

CN Hyaluronic acid, 3-phenyl-2-propenoate (ester), polymer with chondroitin
 hydrogen sulfate 3-phenyl-2-propenoate (9CI) (CA INDEX NAME)

CM 1

CRN 153130-78-0

CMF C9 H8 O2 . x Unspecified

CM 2

CRN 9004-61-9

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 621-82-9

CMF C9 H8 O2

Ph-CH=CH-CO₂H

CM 4

CRN 152787-16-1

CMF C9 H8 O2 . x H2 O4 S . x Unspecified

CM 5

CRN 9007-27-6

CMF Unspecified

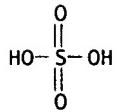
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 6

CRN 7664-93-9

CMF H2 O4 S



CM 7

CRN 621-82-9

CMF C9 H8 O2

Ph-CH=CH-CO₂H

L47 ANSWER 21 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1993:588551 HCPLUS
 DOCUMENT NUMBER: 119:188551
 TITLE: Polyaminocations covalently immobilized on polymeric surfaces with polyethylene oxide spacers for heparin binding
 INVENTOR(S): Mohammad, Syed Fazal; Ma, Xing Hang; Kim, Sung Wan
 PATENT ASSIGNEE(S): University of Utah, USA
 SOURCE: PCT Int. Appl., 41 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9314127	A1	19930722	WO 1993-US678	19930119 <--
	W:	AU, BB, BG, BR, CA, DE, FI, GB, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD		
	RW:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG		
AU 9335926	A1	19930803	AU 1993-35926	19930119 <--
PRIORITY APPLN. INFO.:			US 1992-822715	19920121
			WO 1993-US678	19930119

AB A compn. for removal of heparin from blood to minimize the risk of hemorrhagic complications comprises a polymeric substrate modified to contain primary amino group-contg. polycation ligands covalently bonded to the substrate through a polyethylene oxide spacer. Thus, diacid-terminated polyethylene oxide was coupled onto a cellulose acetate film and polyallylamine was reacted for immobilization. The film was placed in a heparin soln. and its heparin-binding efficacy was demonstrated.

IT 25067-34-9D, Ethylene-vinyl alcohol copolymer, reaction products with PEO deriv. and polyaminocations 26336-38-9D, Polyvinylamine, reaction products with PEO deriv. and cellulose acetate 30551-89-4D, Polyallylamine, reaction products with PEO deriv. and cellulose acetate

RL: BIOL (Biological study)
 (blood treatment with, for heparin removal)

RN 25067-34-9 HCPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

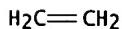
CM 1

CRN 557-75-5
 CMF C2 H4 O



CM 2

CRN 74-85-1
 CMF C2 H4

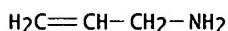


RN 26336-38-9 HCPLUS
 CN Ethenamine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 593-67-9
CMF C2 H5 NRN 30551-89-4 HCPLUS
CN 2-Propen-1-amine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 107-11-9
CMF C3 H7 NIT 9005-49-6, Heparin, biological studies
RL: REM (Removal or disposal); PROC (Process)
(removal of, from blood, by binding with polyaminocations immobilized
on polymeric surfaces with PEO spacers)
RN 9005-49-6 HCPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 22 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1993:208974 HCPLUS
 DOCUMENT NUMBER: 118:208974
 TITLE: A method of screening for inhibitors of
 heparin-binding protein
 INVENTOR(S): Flodgaard, Hans
 PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
 SOURCE: PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9305396	A1	19930318	WO 1992-DK270	19920909 <--
W: AU, CA, CS, FI, HU, JP, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
AU 9226580	A1	19930405	AU 1992-26580	19920909 <--
EP 645016	A1	19950329	EP 1992-920351	19920909 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
JP 07504081	T2	19950511	JP 1992-504849	19920909 <--
PRIORITY APPLN. INFO.:			WO 1991-DK264	19910912
			WO 1992-DK270	19920909

AB Inhibitors of heparin-binding protein (HBP) are screened by incubating HBP, or a cell producing HBP, with a substance suspected of being an HBP inhibitor and with tissue, cells, or a component thereof capable of interacting with HBP, and detecting any effect of the substance on the interaction of HBP with the tissue, cells, or component thereof, decreased interaction indicating that the substance is an HBP inhibitor. Interaction of human HBP with several types of cells is described. Addn. of HBP to PMA-stimulated U937 cells caused a strong homotypic aggregation. Potential HBP inhibitors could be screened using the exptl. conditions described.

IT 9002-86-2, Poly(vinyl chloride) 9002-89-5,

Poly(vinyl alcohol) 9003-20-7, Poly(vinyl acetate)

RL: ANST (Analytical study)

(endothelial or smooth muscle cells or fibroblasts on solid support of, in potential heparin-binding protein inhibitor screening)

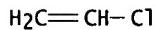
RN 9002-86-2 HCPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4

CMF C2 H3 Cl



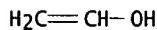
RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O



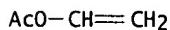
RN 9003-20-7 HCPLUS

CN Acetic acid ethenyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2



IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)

(protein binding, inhibitors of, screening for, alteration of heparin-binding protein interaction with cell or tissue in)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 23 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:154491 HCPLUS

DOCUMENT NUMBER: 118:154491

TITLE: Thrombin and albumin adsorption to PVA and heparin-PVA hydrogels. 2: Competition and displacement

AUTHOR(S): Smith, Barbara A. H.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng., Univ. Toronto, Toronto, ON, MSS 1A4, Can.

SOURCE: Journal of Biomedical Materials Research (1993), 27(1), 89-95

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thrombin adsorption to polyvinyl alc. (PVA) was different from its adsorption to polyethylene (PE), not so much in amt., but in its affinity.

Thrombin was more easily displaced from polyethylene and its adsorption was more readily prevented by prior or simultaneous exposure to albumin. From PVA (or heparin-PVA), only apprx.30% of the adsorbed protein could be removed by a series of eluents, including even harsh ones such as 2.5M NaOH and 6M guanidine; >85% could be removed from PE. Thrombin adsorption to PVA was not affected by the presence of BSA in soln. or at the surface, but was virtually prevented on PE by preexposure to or adsorption with BSA. Heparin-PVA was not much different than PVA in most of these expts., but did exhibit a "Vroman effect". In the absence of fibrinogen or antithrombin III, there was a max. in thrombin adsorption from plasma at a plasma concn. of 1%. The behavior on this surface was dependent on both exposure time and protein concn. These studies highlight the complexity of the interaction between plasma proteins and polymer surfaces (particularly hydrogel surfaces) and the difficulty of obtaining a clear picture of what happens when a single protein interacts with a polymer in the presence of other proteins.

IT 9002-89-5, Poly(vinyl alcohol)

RL: BIOL (Biological study)
(hydrogel, albumin and thrombin adsorption to, heparinization effect on, biomaterials in relation to)

RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



IT 9002-89-5D, Poly(vinyl alcohol), reaction products with heparin 9005-49-6D, Heparin, reaction products with poly(vinyl alc.)

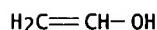
RL: BIOL (Biological study)
(hydrogels, albumin and thrombin adsorption to, biomaterials in relation to)

RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 24 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:27435 HCPLUS

DOCUMENT NUMBER: 118:27435

TITLE: Synthesis of two novel heparinizable polymeric materials starting from an ethylene/vinyl alcohol/vinyl acetate terpolymer

AUTHOR(S): Barbucci, Rolando; Benvenuti, Manuela; Magnani, Agnese; Tempesti, Federica

CORPORATE SOURCE: Dep. Chem., Siena, 53100, Italy

SOURCE: Makromolekulare Chemie (1992), 193(12), 2979-88

CODEN: MACEAK; ISSN: 0025-116X

DOCUMENT TYPE: Journal
LANGUAGE: English

AB A partially hydrolyzed ethylene/vinyl acetate (EVA) copolymer was modified through the covalent binding of a heparin-complexing polymer, in order to improve its blood compatibility. Two different heparinizable polymeric materials (EVAPA I and II) were obtained by a two-step reaction between an ethylene/vinyl alc./vinyl acetate (EVALVA) terpolymer and a poly(amido-amide) (N2LL) using either hexamethylene diisocyanate (HMDI) or 1,1'-carbonyldiimidazole (CDI) as bifunctional agents, resp. EVALVA terpolymer was prep'd. by a homogeneous sapon. process, and the percentage of hydrolysis was detd. by an anal. method. EVAPA I and II syntheses were followed by FT-IR/ATR (Fourier Transform IR/Attenuated Total Reflection) spectroscopy.

IT 25067-34-9DP, Ethylene-vinyl alcohol copolymer, sapond., reaction products with acetic anhydride and polyamidoamine
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. and heparinization of, for biomaterials)

RN 25067-34-9 HCAPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

 $\text{H}_2\text{C}=\text{CH}-\text{OH}$

CM 2

CRN 74-85-1

CMF C2 H4

 $\text{H}_2\text{C}=\text{CH}_2$

IT 9005-49-6DP, Heparin, reaction products with polymer contg. sapond. ethylene-vinyl alc. copolymer and polyamidoamine
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of, for biomaterials)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9041-08-1, Heparin sodium

RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with polymer contg. sapond. ethylene-vinyl alc. copolymer and polyamidosamine, for biomaterials)

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 25 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1992:518449 HCAPLUS

DOCUMENT NUMBER: 117:118449

TITLE: Heparin-poly(ethylene glycol)-poly(vinyl alcohol) hydrogel:
preparation and assessment of thrombogenicity

AUTHOR(S): Llanos, Gerard R.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,

SOURCE: ON, M5S 1A4, Can.
 Biomaterials (1992), 13(7), 421-4 ←
 CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Heparin was immobilized on to poly(vinyl alc.) (PVA) hydrogel through the free isocyanate end-group on a polyethylene glycol (PEG2000) which had been previously covalently linked to the hydrogel via a urethane moiety. The intention was to reduce the platelet reactivity of the PVA while also suppressing fibrin formation. Elemental nitrogen anal. revealed that the total amt. of bound heparin was 19 .mu.mol/g of dried gel. An increase in the in vitro whole blood clotting time of PVA was obsd. This was attributed to bound heparin, as the elution rate of heparin from the gel (23 pmol/m2 min) was too low to produce a significant bulk concn. to interfere with fibrin formation. Ex vivo assessment using a chronic canine A-V shunt showed that the bound heparin hydrogel had no effect on the drop in the no. of platelets induced by PVA hydrogel, but increased the fractional rate of platelet destruction from approx. 0.35/day to an av. value of 0.42/day.

IT 9002-89-5DP, Polyvinyl alcohol, reaction products with polyethylene glycol and heparin 9005-49-6DP,
 Heparin, reaction products with polyethylene glycol and poly(vinyl alc.)
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (hydrogels, prepn. and antithrombogenicity of, for biomaterials)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 26 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1992:433735 HCPLUS
 DOCUMENT NUMBER: 117:33735
 TITLE: Nonthrombogenic glycosaminoglycan copolymers for medical goods
 INVENTOR(S): Mazid, M. Abdul; Unger, Frank M.
 PATENT ASSIGNEE(S): Chembomed Ltd., Can.
 SOURCE: PCT Int. Appl., 60 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9115252	A1	19911017	WO 1991-CA120	19910410 <--
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US				←
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2080241	AA	19911011	CA 1991-2080241	19910410 <--
AU 9175637	A1	19911030	AU 1991-75637	19910410 <--
EP 524209	A1	19930127	EP 1991-906943	19910410 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
 JP 05507298 T2 19931021 JP 1991-506427 19910410 <--
 PRIORITY APPLN. INFO.: US 1990-507230 19900410
 WO 1991-CA120 19910410

AB Biocompatible glycosaminoglycan copolymers which are antithrombotic and antithrombogenic are provided for biomedical applications requiring long-term or permanent maintenance of anticoagulant properties. The novel copolymers of the invention are comprised of small fragments or segment of glycosaminoglycans such as heparin (I), which is produced by enzymic or chem. means, and copolymerd. with synthetic monomeric components. Low mol. wt. I, obtained by deaminative cleavage with NO2H, was copolymerd. with 2-aminoethyl methacrylate and acrylamide to obtain an antithrombotic polymer. The ratio of antifactor Xa to activated partial thromboplastin time (indicating antithrombotic activity with respect to its anticoagulant activity) of the copolymer was 19.7.

IT 138781-13-2P 138781-14-3P 138781-16-5P
 138781-18-7P 138781-19-8P 138781-21-2P
 138781-22-3P

RL: PREP (Preparation)
 (prepn. of, for antithrombogenic medical goods)

RN 138781-13-2 HCPLUS

CN Heparin, polymer with ethenylbenzene, graft (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
 CMF C8 H8

$\text{H}_2\text{C}=\text{CH}-\text{Ph}$

RN 138781-14-3 HCPLUS
 CN Heparin, polymer with 2-hydroxyethyl 2-methyl-2-propenoate and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

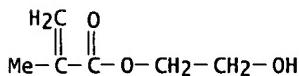
CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

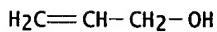
CM 2

CRN 868-77-9
 CMF C6 H10 O3



CM 3

CRN 107-18-6
 CMF C3 H6 O



RN 138781-16-5 HCPLUS
 CN Heparin, polymer with 1-ethenyl-2-pyrrolidinone and 2-propenamide, graft (9CI) (CA INDEX NAME)

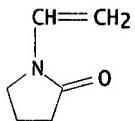
CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

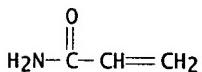
CM 2

CRN 88-12-0
 CMF C6 H9 N O



CM 3

CRN 79-06-1
 CMF C3 H5 N O



RN 138781-18-7 HCPLUS
 CN Heparin, polymer with N,N'-methylenebis[2-propenamide], 2-propenamide and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

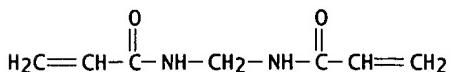
CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

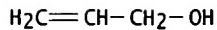
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

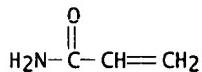
CRN 110-26-9
 CMF C7 H10 N2 O2



CM 3

CRN 107-18-6
CMF C3 H6 O

CM 4

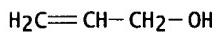
CRN 79-06-1
CMF C3 H5 N ORN 138781-19-8 HCPLUS
CN Heparin, polymer with 2-propenenitrile and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

CM 1

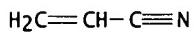
CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 107-18-6
CMF C3 H6 O

CM 3

CRN 107-13-1
CMF C3 H3 NRN 138781-21-2 HCPLUS
CN Heparin, polymer with 4-ethenylbenzenesulfonic acid, graft (9CI) (CA INDEX NAME)

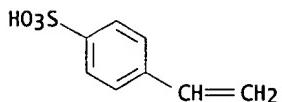
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 98-70-4
 CMF C8 H8 O3 S



RN 138781-22-3 HCPLUS
 CN Heparin, polymer with ethenyl acetate, graft (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 108-05-4
 CMF C4 H6 O2

AcO—CH=CH₂

L47 ANSWER 27 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1992:11171 HCPLUS
 DOCUMENT NUMBER: 116:11171
 TITLE: Synthesis and nonthrombogenicity of polyetherurethaneurea film grafted with poly(sodium vinyl sulfonate)
 AUTHOR(S): Ito, Yoshihiro; Iguchi, Yuichiro; Kashiwagi, Takashi;
 Imanishi, Yukio
 CORPORATE SOURCE: Dep. Polym. Chem., Kyoto Univ., Kyoto, 606, Japan
 SOURCE: Journal of Biomedical Materials Research (1991
), 25(11), 1347-61
 CODEN: JBMRBG; ISSN: 0021-9304
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Synthesis of nonthrombogenic materials without using biol. active substances were explored. Poly(sodium vinyl sulfonate) is a water-sol. synthetic polymer and activates antithrombin III to exert nonthrombogenicity that was dependent on the mol. wt. Polyetherurethaneurea film was plasma-treated and graft-polymd. with sodium vinyl sulfonate. The graft film showed excellent in vitro and ex vivo nonthrombogenicity by suppressing in interactions with plasma proteins and platelets as well as by inactivating blood-clotting factors.
 IT 9005-49-6, Heparin, biological studies
 RL: BIOL (Biological study)
 (-like activity, of poly(sodium vinyl sulfonate), nonthrombogenic biomaterials in relation to)
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)
 *** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 IT 9002-89-5, Poly(vinyl alcohol)
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anticoagulant activity of, biomaterial coating in relation to)
RN 9002-89-5 HCPLUS
CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

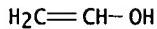
L47 ANSWER 28 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:663374 HCPLUS
DOCUMENT NUMBER: 115:263374
TITLE: Heparin binding on poly(L-lysine)-immobilized surface
AUTHOR(S): Ma, Xinghang; Mohammad, Syed Fazal; Kim, Sung Wan
CORPORATE SOURCE: Cent. Controlled Chem. Delivery, Univ. Utah, Salt Lake City, UT, 84108, USA
SOURCE: Journal of Colloid and Interface Science (1991), 147(1), 251-61
CODEN: JCISA5; ISSN: 0021-9797
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A poly(ethylene-vinyl alc.) (PEVAL) copolymer surface with immobilized poly(L-lysine).HBr (PLL.HBr) has been used as a model surface to study the interaction of heparin with polycationic surfaces. The amt. of heparin bound from PBS was 0.52 .mu.g/cm³ on a smooth PL-immobilized PEVAL surface and 1.69 .mu.g/cm³ on a porous PLL-PEVAL surface. Heparin adsorption kinetic studies indicated that heparin adsorption from plasma or blood exhibited a "two step" profile, which may be related to the effects of competitive binding between heparin and proteins, membrane porosity, and soln. viscosity. The time needed to reach heparin binding satn. was 10 min in BPS and 30 min in plasma or blood at flow rate of 100 mL/min. However, under similar exptl. conditions, heparin binding in PBS did not reach satn. for 2 h at flow rate of 3 mL/min. The difference in time required to reach satn. for two different flow rates (3 and 100 mL/min) was attributed to the heparin concn. gradient between bulk and surface. Bound heparin was eluted with a basic soln.. The recovery of heparin bound from PBS, plasma, and blood was 85%, which implied that most of the heparin was tightly bound to protonated amino groups on the side chain of PLL. The data suggest that electrostatic interactions between heparin and PLL may be the driving force for heparin binding. This study offers information for understanding heparin binding onto polycationic surfaces, esp. in biol. systems.
IT 9005-49-6, Heparin, properties
RL: PRP (Properties)
(binding of, to polycationic surfaces, antithrombogenic biomaterials in relation to)
RN 9005-49-6 HCPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 25067-34-9DP, reaction product with polylysine
RL: SPN (Synthetic preparation); PREP (Preparation)
/heparin binding and prepn. of, antithrombogenic biomaterials in relation to/
RN 25067-34-9 HCPLUS
CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O



CM 2

CRN 74-85-1
CMF C2 H4



IT 25067-34-9
RL: BIOL (Biological study)
(polylysine immobilization on, for heparin binding study)
RN 25067-34-9 HCPLUS
CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



CM 2

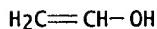
CRN 74-85-1
CMF C2 H4



IT 9002-89-5
RL: BIOL (Biological study)
(vinal fibers, ethylene-vinyl alc., polylysine
immobilization on, for heparin binding study)
RN 9002-89-5 HCPLUS
CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



L47 ANSWER 29 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:519995 HCPLUS
DOCUMENT NUMBER: 115:119995
TITLE: Platelet consumption by polyvinyl alcohol coated
tubing in canines
AUTHOR(S): Ip, W. F.; Sefton, M. V.
CORPORATE SOURCE: Cent. Biomater., Univ. Toronto, Toronto, ON, M5S 1A4,
Can.

SOURCE: Journal of Biomedical Materials Research (1991), 25(7), 875-87
 CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Poly(vinyl alc.) (PVA)-coated polyethylene tubing, with or without immobilized heparin, caused severe thrombocytopenia and enhanced the prodn. of new platelets when inserted in a chronic arteriovenous shunt in canines. A similar length of uncoated polyethylene tubing neither led to thrombocytopenia nor significantly enhanced platelet regeneration, relative to the shunt only without a test section. Platelet regeneration was monitored by the malondialdehyde assay, which was assumed to make a distinction between new and old platelets. This distinction was combined with the platelet count values to enable calcn. of the cumulative consumption curve and the initial fractional consumption rate in the presence of a nonconstant platelet count. The resulting initial fractional consumption rates were: 34%/day for PVA, 20.5%/day for polyethylene, and 18%/day for the shunt only blank.

IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)
 (blood platelet consumption by poly(vinyl alc.)-coated polyethylene tubing in relation to)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-89-5, Poly(vinyl alcohol)

RL: BIOL (Biological study)
 (polyethylene tubing coated with, blood platelets consumption by, heparin effect on)

RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H2C=CH-OH

L47 ANSWER 30 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1991:254081 HCPLUS

DOCUMENT NUMBER: 114:254081

TITLE: Manufacture of antithrombogenic medical goods from heparin-bound poly(vinyl chloride) derivatives

INVENTOR(S): Saito, Noboru; Kashiwagi, Nobuyoshi; Sasaki, Masatomi

PATENT ASSIGNEE(S): Terumo Corp., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03037073	A2	19910218	JP 1989-173187	19890705 <--

PRIORITY APPN. INFO.: JP 1989-173187 19890705

AB Antithrombogenic medical goods are prepd. from chem. modified poly(vinyl chloride) to which heparin is bound via a coupling agent. Thus, a sheet was prepd. from NH₂-group-contg. poly(vinyl chloride) and treated with a soln. contg. heparin and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl

to give an antithrombogenic sheet, which may be used in an app. for extracorporeal blood circulation and blood filtration.

IT 9005-49-6D, Heparin, poly(vinyl chloride)
deriv.-bound
RL: BIOL (Biological study)
(for antithrombogenic medical goods)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-86-2D, Poly(vinyl chloride), aminated,
heparin-bound
RL: BIOL (Biological study)
(medical goods manuf. from, antithrombogenic)

RN 9002-86-2 HCPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4
CMF C2 H3 Cl $\text{H}_2\text{C}=\text{CH}-\text{Cl}$

L47 ANSWER 31 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1990:618143 HCPLUS
 DOCUMENT NUMBER: 113:218143
 TITLE: Inactivation of thrombin in heparin-PVA
coated tubes
 AUTHOR(S): Rollason, G.; Sefton, M. V.
 CORPORATE SOURCE: Cent. Biomater., Univ. Toronto, Toronto, ON, M5S 1A4,
Can.
 SOURCE: Journal of Biomaterials Science, Polymer Edition (1989), 1(1), 31-41
 CODEN: JBSEEA; ISSN: 0920-5063
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Heparin, immobilized on polyvinyl alc. by reaction with glutaraldehyde (heparin-PVA), retained its ability to accelerate the antithrombin III inactivation of thrombin, in a recirculating flow loop using heparin-PVA coated polyethylene tubes. The extent of inactivation, for a const. flow time, was approx. const. over ten cycles of exposure to thrombin and antithrombin III, suggesting that the immobilized heparin was reusable, as expected from the catalytic nature of non-immobilized heparin. Assessment of the chromogenic substrate activity of adsorbed thrombin and the extent of displacement were less conclusive with the implication that thrombin is adsorbed to heparin-PVA or PVA without heparin in multiple states.

IT 9002-89-5D, Poly(vinyl alcohol), reaction products with heparin 9005-49-6D, Heparin, reaction products with poly(vinyl alc.)
RL: BIOL (Biological study)
(polyethylene tubing coated with, inactivation of thrombin on, biomaterials in relation to)

RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O $\text{H}_2\text{C}=\text{CH}-\text{OH}$

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 32 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1990:597870 HCPLUS
 DOCUMENT NUMBER: 113:197870
 TITLE: Platelet consumption by poly(vinyl alcohol) (PVA)
 hydrogels and modified PVA surfaces
 AUTHOR(S): Sefton, M. V.; Llanos, G.; Ip, W. F.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
 ON, M5S 1A4, Can.
 SOURCE: Polymeric Materials Science and Engineering (1990), 62, 741-5
 CODEN: PMSEDG; ISSN: 0743-0515
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB PVA hydrogels were prep'd. by covalent coupling of glutaraldehyde with PVA in the presence of MgCl₂. Heparin was bound to these hydrogels. The interaction of heparin-PVA with blood platelets was dominated by the reactivity of the underlying substrate (PVA), the platelets appear to be consumed after transient contact with PVA (or heparin-PVA) and polyethylene oxide (PEO) was immobilized onto the PVA hydrogel by using aldehyde-terminated PEO. The PEO modification resulted in albumin adsorption and a slight redn. in consumption. Thus, PEO does not appear to be effective in reducing the platelet reactivity of PVA.

IT 9002-89-5, Poly(vinyl alcohol) 9002-89-5D, Poly(vinyl alcohol), reaction products with heparin
 9005-49-6D, Heparin, reaction products with poly(vinyl alc.) hydrogels
 RL: BIOL (Biological study)
 (blood platelet consumption by)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 33 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:558687 HCPLUS
 DOCUMENT NUMBER: 113:158687
 TITLE: Controlled-release systems containing heparin
 and growth factors
 INVENTOR(S): Edelman, Elazer R.; Langer, Robert S.; Klagsburn,
 Michael; Mathiowitz, Edith
 PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
 SOURCE: PCT Int. Appl., 24 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 8912464	A1	19891228	WO 1989-US2575	19890613 <--	
W: JP					
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
US 5100668	A	19920331	US 1988-206520	19880614 <--	
PRIORITY APPLN. INFO.:			US 1988-206520	19880614	
AB	A system for stabilizing fibroblast-derived growth factors (FGF), maintaining their bioactivity over a prolonged period of time, and controllably releasing them for use is disclosed. The system uses growth factors bound to biocompatible substrates via heparin or heparin-derived compds. to maintain the bioactivity of the growth factors. A growth factor bound to a heparin-coated substrate can be used independently as a controlled-release device, or can be incorporated into a reservoir or matrix type controlled-release device to further enhance the controlled-release properties. FGF complexed to heparin-dextran beads and encapsulated in Na alginate capsules (allowed to harden for 5 min) was released at .apprx.1 unit/day. The released FGF retained .apprx.85% activity as detd. by a 3T3 cell synthesis assay. The release rate was .apprx.2 units/day for FGF complexed to heparin-Sepharose beads. The released FGF retained .apprx.25% activity.				
IT	9005-49-6D, Heparin, carrier conjugates, complexes with fibroblast-derived growth factor RL: BIOL (Biological study) (as controlled-release device for growth factor)				
RN	9005-49-6 HCPLUS				
CN	Heparin (8CI, 9CI) (CA INDEX NAME)				
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***					
IT	24937-78-8, Ethylene-vinyl acetate copolymer RL: BIOL (Biological study) (fibroblast-derived growth factor complex with heparin -carrier conjugate encapsulation with, for controlled release system)				
RN	24937-78-8 HCPLUS				
CN	Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)				

CM 1

CRN 108-05-4
CMF C4 H6 O2AcO—CH=CH₂

CM 2

CRN 74-85-1
CMF C2 H4

$\text{H}_2\text{C}=\text{CH}_2$

L47 ANSWER 34 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1990:479111 HCPLUS
 DOCUMENT NUMBER: 113:79111
 TITLE: Improved synthesis of polystyrene-poly(ethylene oxide)-heparin block copolymers
 AUTHOR(S): Vulic, I.; Loman, A. J. B.; Feijen, J.; Okano, T.; Kim, S. W.
 CORPORATE SOURCE: Dep. Chem. Technol., Univ. Twente, Enschede, Neth.
 SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry
 (1990), 28(7), 1693-720
 CODEN: JPACEC; ISSN: 0887-624X

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Amino-semitelechelic polystyrene was prep'd. by anionic polymn. of styrene in cyclohexane, using sec-BuLi as initiator and N-(benzylidene)trimethylsilyl amide as terminator. After purifn., polystyrene with one amino group per chain and a narrow mol. wt. distribution was obtained. The terminal amino group was used in the coupling reaction with amino-telechelic poly(ethylene oxide) using 2,4-TDI to produce amino-semitelechelic polystyrene-poly(ethylene oxide) diblock copolymer (I). Polystyrene-poly(ethylene oxide)-heparin triblock copolymer was synthesized in a DMF-H₂O (40:1) mixt. by a coupling reaction of I with HNO₂-degraded heparin at pH 7 in the presence of NaBH₃CN via reductive amination. Using this procedure, 18-32% heparin was incorporated, corresponding to .+-1 I chain per heparin mol.

IT 114954-84-6P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and characterization of)

RN 114954-84-6 HCPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
 CMF C8 H8

$\text{H}_2\text{C}=\text{CH}-\text{Ph}$

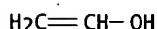
CM 3

CRN 75-21-8
 CMF C2 H4 O

0

L47 ANSWER 35 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1989:219044 HCPLUS
 DOCUMENT NUMBER: 110:219044
 TITLE: In vitro platelet interactions with a heparin
 -polyvinyl alcohol hydrogel
 AUTHOR(S): Cholakis, Cynthia H.; Sefton, Michael V.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
 ON, M5S 1A1, Can.
 SOURCE: Journal of Biomedical Materials Research (1989
), 23(4), 399-415 ←
 CODEN: JBMRBG; ISSN: 0021-9304
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB No difference in in vitro platelet reactivity was found between an
 immobilized heparin contg. hydrogel [heparin-poly(vinyl alc.)(PVA)] and
 the hydrogel without heparin, in a variety of exptl. assays. There was no
 significant difference between the heparin-PVA- and PVA-coated
 polyethylene tubing in the no. of 51Cr-labeled platelets, the extent of
 [14C]serotonin release by the adherent platelets or in the degree of
 platelet count decrease after 1 h exposure to citrated canine whole blood
 in a Chandler loop system. Furthermore, adhesion and release values were
 lower than those obsd. with the uncoated polyethylene tubing (e.g., 9.3
 platelets/103 .mu.g2 on PVA; 18.3 platelets/103 .mu.m2 on polyethylene).
 There was also no significant difference between heparin-PVA and PVA in
 bead column retention values with canine blood and with the previously
 reported washed human platelet adhesion/release values. Thus there
 appears to be no effect of the immobilized heparin by itself on the in
 vitro interactions of PVA with platelets, with the reactivity towards
 platelets dominated by that of the underlying substrate (i.e., PVA).
 IT 9002-89-5D, Poly(vinyl alcohol), reaction products with
 heparin 9005-49-6D, Heparin, reaction products
 with poly(vinyl alc.)
 RL: BIOL (Biological study)
 (hydrogels, interaction of, with blood platelets)
 RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 36 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1989:199150 HCPLUS
 DOCUMENT NUMBER: 110:199150
 TITLE: Effect of heparin-PVA hydrogel on platelets
 in a chronic canine arterio-venous shunt
 AUTHOR(S): Cholakis, Cynthia H.; Zingg, Walter; Sefton, Michael
 V.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
 ON, M5S 1A4, Can.
 SOURCE: Journal of Biomedical Materials Research (1989
), 23(4), 417-41 ←
 CODEN: JBMRBG; ISSN: 0021-9304
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Polyvinyl alc. (PVA) hydrgel, with or without heparin, was reactive

towards canine platelets in a chronic arteriovenous shunt as demonstrated by an increase in platelet regeneration time, a systemic decrease in platelet count and transient decrease in platelet serotonin content. Immobilized heparin (heparin-PVA) had no effect whereas unmodified polyethylene was unreactive despite similar levels of platelet deposition as measured by SEM and a higher *in vitro* reactivity. Twenty-centimeter lengths of hydrogel coated polyethylene tubing were inserted between the arterial and venous portions of the shunt and left in place for 4-6 days, without the complicating artifacts of anticoagulation, anesthesia, or surgical intervention. Regeneration time was measured as the return to normal platelet cyclooxygenase activity after a single 240-mg dose of aspirin, with cyclooxygenase activity measured *in vitro* as malondialdehyde prodn. Although measuring new platelet prodn., regeneration time is an indirect measure of platelet consumption, so that the reduced regeneration time seen here was presumed to reflect enhanced material assocd. consumption and thromboembolism. Like other hydrogels, PVA does not appear to bee "thrombodherent" but it does appear thrombogenic. Immobilized heparin had no addnl. effect, presumably because the platelet response was dominated by the reactivity of the underlying substrate.

IT 9002-89-5, Polyvinyl alcohol
RL: BIOL (Biological study)

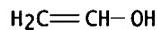
(heparin immobilized on, hydrogels, blood platelets on
arteriovenous shunt response to)

RN 9002-89-5 HCPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)
(immobilized on poly(vinyl alc.) hydrogels, blood platelet in
arteriovenous shunt response to)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 37 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:179466 HCPLUS

DOCUMENT NUMBER: 110:179466

TITLE: Activity toward thrombin-antithrombin of
heparin immobilized on two hydrogels

AUTHOR(S): Tay, S. W.; Merrill, E. W.; Salzman, E. W.; Lindon, J.

CORPORATE SOURCE: Dep. Chem. Eng., MIT, Cambridge, MA, USA

SOURCE: Biomaterials (1989), 10(1), 11-15

CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Com. obtained (Diosynth) heparin was covalently bonded to poly(vinyl alc.) (PVA) hydrogels and to polyethylene oxide (PEO) hydrogels activated by tresyl chloride. As tresyl chloride activation of PVA increased, the specific activity of the bound heparin toward thrombin and antithrombin decreased by nearly a factor of 10 and that com. heparin bound to PEO had nearly 10-fold greater activity than when bound to PVA at comparable concns. These findings suggest that the long leash provided by PEO hydrogels may give the heparin more access to the thrombin-antithrombin pair than the tight bond to PVA, and that crowding of heparin units on a surface limits access of the thrombin-antithrombin pair.

IT 9002-89-5DP, Polyvinyl alcohol, reaction products with

heparin 9005-49-6DP, Heparin, reaction products with p-lyethylene oxide or poly(vinyl alc.)
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and activity towards thrombin-antithrombin of)

RN 9002-89-5 HCPLUS
CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



RN 9005-49-6 HCPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 38 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1989:115443 HCPLUS
DOCUMENT NUMBER: 110:115443
TITLE: Synthesis and characterization of polystyrene-poly(ethylene oxide)-heparin block copolymers [Erratum to document cited in CA109(2):7066d]
AUTHOR(S): Vulic, I.; Okano, T.; Kim, S. W.; Feijen, J.
CORPORATE SOURCE: Dep. Chem. Technol., Twente Univ. Technol., Enschede, Neth.
SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry (1989), 27(1), 397
CODEN: JPACEC; ISSN: 0887-624X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Errors in the addresses of the authors have been cor. The error was not reflected in the abstr. or the index entries.
IT 114954-84-6P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and properties of (Erratum))
RN 114954-84-6 HCPLUS
CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

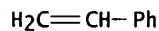
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
CMF C8 H8



CM 3

CRN 75-21-8
CMF C2 H4 O

0

L47 ANSWER 39 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1989:82452 HCPLUS
 DOCUMENT NUMBER: 110:82452
 TITLE: Binding of heparin onto ethylene-vinyl alcohol copolymer membrane
 AUTHOR(S): Shiomi, Tomoo; Satoh, Mikitoshi; Miya, Masamitsu;
 Imai, Kiyokazu; Akasu, Hiroyuki; Otake, Kazuhiko
 CORPORATE SOURCE: Dep. Mater. Sci. Technol., Technol. Univ. Nagaoka,
 Nagaoka, 940-21, Japan
 SOURCE: Journal of Biomedical Materials Research (1988) ← BT/M1C
), 22(A3), 269-80
 CODEN: JBMRBG; ISSN: 0021-9304
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Heparin was ionically bound onto the surface of an ethylene-vinyl alc. copolymer (EVAL) membrane which was derivatized by aminoacetalization to produce cationic surface charges. The amt. of bound heparin was proportional to the ion exchange capacity of the aminoacetalized membrane and the maximal amt. obtained in this expt. was 96 U/cm² (0.59 mg/cm²). Plasma recalcification times were measured for the heparinized membrane thus obtained. Recalcification times increased proportionally with the amt. of heparin bound on the membrane, while original EVAL membranes and the non-heparinized aminoacetalized membrane did not show increases in recalcification times. This means that the heparinized EVAL membrane has a more nonthrombogenic property due to the release of heparin. The apparent amt. of heparin released from the membrane into plasma was estd. from plasma recalcification times. The release rate was 0.30-0.33 U/cm²/h (1.8 .times. 10-3-2.0 .times. 10-3 mg/cm²/h) for the membranes whose surface was considered to be satd. with heparin. The release amt. was .apprx.0.6% compared to the adsorbed heparin in the case of the 96 U/cm²-heparinized membrane incubated in plasma for 60 min.

IT 9041-08-1, Sodium heparin
 RL: PROC (Process)
 (binding of, to aminoacetalized ethylene-vinyl alc.
 copolymer membrane, thrombogenicity in relation to)

RN 9041-08-1 HCPLUS
 CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 IT 25067-34-9D, EVAL, aminoacetalized
 RL: BIOL (Biological study)
 (membrane, heparin binding to, thrombogenicity in relation
 to)
 RN 25067-34-9 HCPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

H₂C=CH-OH

CM 2

CRN 74-85-1

CMF C2 H4



L47 ANSWER 40 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1988:498879 HCPLUS
 DOCUMENT NUMBER: 109:98879
 TITLE: A method for manufacturing a hydrophilic and heparin-containing polymer with an improved antithrombogenic property
 INVENTOR(S): Imai, Kyokazu; Shiomi, Tomoo; Miya, Masamitsu; Akasu, Hiroyuki; Otake, Kazuhiko
 PATENT ASSIGNEE(S): Kuraray Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62260802	A2	19871113	JP 1986-105695	19860507 <-- <i>[Signature]</i>
JP 06078382	B4	19941005		

PRIORITY APPLN. INFO.: JP 1986-105695 19860507

AB . The title method involves ionically bonding heparin to an amino-group-contg. polymer prep'd. by carrying out the reaction between a polymer having OH groups and RR₁NZCHO [R,R₁ = H or (un)substituted C₁-12 alkyl; and Z = (un)substituted C₄-20 alkylene or alkenyl-contg. at. group having \geq 4 chain length] or its acetal compd. A fiber (15 μm) 0.4 g of ethylene-vinyl alc. copolymer (sapon. degree \geq 99.9%) contg. ethylene 32 mol% was dipped in an aq. soln. contg. 3-(N,N-dimethylaminopropanediamine)propionaldehyde di-Me acetal 2.5, HCl 8.0, and H₂O 73 g, subjected to a reaction at 50.degree. for 2 h, washed with a large amt. of H₂O, and dipped in an aq. soin. (55.degree.) contg. 0.1 N NaCl and heparin for 3 days to effect heparin bonding. The film showed delaying of coagulation of bovine blood serum.

IT 9005-49-6DP, Heparin, salts, reaction products of amino acetals and saponid. ethylene-vinyl acetate copolymer
 24937-78-8DP, Ethylene-vinyl acetate copolymer, saponid., reaction product with amino acetals, heparinated

RL: PREP (Preparation)
 (manuf. of, as prosthetic)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

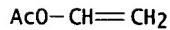
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
 CMF C4 H6 O2



CM 2

CRN 74-85-1

CMF C2 H4



L47 ANSWER 41 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1988:407066 HCPLUS
 DOCUMENT NUMBER: 109:7066
 TITLE: Synthesis and characterization of polystyrene-poly(ethylene oxide)-heparin block copolymers
 AUTHOR(S): Vulic, I.; Okano, T.; Kim, S. W.; Feijen, J.
 CORPORATE SOURCE: Dep. Chem. Technol., Twente Univ. Technol., Enschede, Neth.
 SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry (1988), 26(2), 381-91
 CODEN: JPACEC; ISSN: 0887-624X
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A procedure for the prepn. of block copolymers composed of a hydrophobic block of polystyrene, a hydrophilic spacer-block of poly(ethylene oxide) and a bioactive block of heparin was investigated. Polystyrene with one amino group per chain was synthesized by free radical oligomerization of styrene in DMF, using 2-aminoethanethiol as a chain transfer agent. This amino group was used in the coupling reaction with amino-telechelic poly(ethylene oxide) to produce an AB type diblock copolymer (I) with one amino group per polystyrene-poly(ethylene oxide) chain. The coupling of I with heparin was performed in a DMF-H2O mixt., first by activating the heparin carboxylic groups with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl at pH 5.1-5.2 and subsequently reacting the activated carboxylic groups with the amino groups of at pH 7.5.

IT 114954-84-6P

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and properties of)

RN 114954-84-6 HCPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

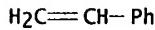
CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
 CMF C8 H8



CM 3

CRN 75-21-8
 CMF C2 H4 O

0


L47 ANSWER 42 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1987:605193 HCPLUS
 DOCUMENT NUMBER: 107:205193
 TITLE: Drug delivery systems based on hyaluronan, derivatives thereof and their salts and method of producing same
 INVENTOR(S): Balazs, Endre A.; Larsen, Nancy E.; Leshchiner, Adolf
 PATENT ASSIGNEE(S): Biomatrix, Inc., USA
 SOURCE: Eur. Pat. Appl., 30 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 224987	A2	19870610	EP 1986-306046	19860805 <--
EP 224987	A3	19871119		
EP 224987	B1	19920415		
R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
AU 8660903	A1	19870604	AU 1986-60903	19860805 <--
AU 595524	B2	19900405		
CA 1340199	A1	19981215	CA 1986-516770	19860825 <--
JP 62129226	A2	19870611	JP 1986-219096	19860916 <--
JP 06092320	B4	19941116		

PRIORITY APPLN. INFO.: US 1985-804178 19851129
 AB Hyaluronic acid and its derivs. are used for sustained-release of pharmaceutical substances. It may be crosslinked with divinyl sulfone, or may be a viscoelastic putty. It is useful for topical products such as eye drops. Na hyaluronate 0.58 g was swelled with water 20 mL for 20 h and treated with aq. NaOH and crosslinked with divinylsulfone. The gel was placed in an NaCl-phosphate buffer and dialyzed against 0.15 M NaCl for 5 days. The crosslinked hyaluronic acid concn. was 0.21%; this gel was mixed with mydriacyl to a concn. of 0.5%. Rabbits treated with this mydriacyl-hyaluronic acid compn. maintained a >50% pupil size increase for apprx. 340 min., compared to 240 min. for controls treated with mydriacyl in salts soln. The role of pupil size decrease was also slower in test rabbits, indicating the combination of a drug with hyaluronic acid gel significantly prolonged the period of effectiveness of the drug.

IT 111307-33-6P

RL: PREP (Preparation)

(prepn. of, for sustained drug release system)

RN 111307-33-6 HCPLUS

CN Hyaluronic acid, sodium salt, polymer with chondroitin hydrogen sulfate and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 9067-32-7

CMF Unspecified

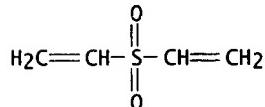
CCI PMS, MAN

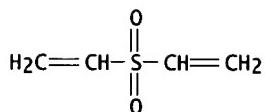
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0

CMF C4 H6 O2 S





CM 3

CRN 9007-28-7
 CMF H2 O4 S . x Unspecified

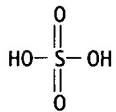
CM 4

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 7664-93-9
 CMF H2 O4 S



L47 ANSWER 43 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1986:632207 HCPLUS
 DOCUMENT NUMBER: 105:232207
 TITLE: Crosslinked gels of hyaluronic acid and products containing these gels for cosmetics and pharmaceuticals
 INVENTOR(S): Balazs, Endre A.; Leshchiner, Adolf
 PATENT ASSIGNEE(S): Biomatrix, Inc., USA
 SOURCE: U.S., 10 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4582865	A	19860415	US 1984-678895	19841206 <--
US 4636524	A	19870113	US 1985-709977	19850308 <--
CA 1230186	A1	19871208	CA 1985-481055	19850508 <--
GB 2168067	A1	19860611	GB 1985-12072	19850513 <--
GB 2168067	B2	19890607		
AU 8543045	A1	19860612	AU 1985-43045	19850528 <--
AU 569157	B2	19880121		
FR 2574414	A1	19860613	FR 1985-7941	19850528 <--
FR 2574414	B1	19870703		
DE 3520008	A1	19860619	DE 1985-3520008	19850604 <--
DE 3520008	C2	19911010		
JP 61138601	A2	19860626	JP 1985-147612	19850704 <--
JP 04030961	B4	19920525		
SE 8503486	A	19860607	SE 1985-3486	19850715 <--

SE 460792	B	19891120		
SE 460792	C	19900315		
US 4605691	A	19860812	US 1985-755976	19850718 <--
GB 2181147	A1	19870415	GB 1986-18719	19860731 <--
GB 2181147	B2	19890607		
GB 2181148	A1	19870415	GB 1986-18720	19860731 <--
GB 2181148	B2	19890607		
AU 8772173	A1	19870827	AU 1987-72173	19870428 <--
AU 572419	B2	19880505		
GB 2205848	A1	19881221	GB 1988-17772	19880726 <--
GB 2205848	B2	19890524		
SE 8901672	A	19890510	SE 1989-1672	19890510 <--
SE 501828	C2	19950522		
JP 02138346	A2	19900528	JP 1989-232667	19890906 <--
JP 06037575	B4	19940518		
US 5128326	A	19920707	US 1990-559413	19900723 <--
PRIORITY APPLN. INFO.:			US 1984-678895	19841206
			US 1985-709977	19850308
			GB 1985-12072	19850513
			US 1985-755976	19850718
			US 1985-804178	19851129
			US 1988-140877	19880106
			US 1989-320822	19890309

AB Mixed crosslinked gels of hyaluronic acid and .gtoreq.1 other hydrophilic polymer having a functional group capable of reacting with divinyl sulfone is prep'd. by subjecting a mixt. of Na hyaluronate and the other hydrophilic polymer in a dil. aq. alk. soln. at a pH .gtoreq.9 to a crosslinking reaction with divinyl sulfone at .apprx.20.degree.. The gels may contain an inert water-insol. substance, e.g., a hydrocarbon, an oil or fat, a pigment, polyethylene, or poly(tetrafluoroethylene), or covalently bonded low mol. wt. substances such as drugs, esp. carminic acid. These products are useful in cosmetic formulations and as drug delivery systems. Thus, a cosmetic formulation contained crosslinked gel 90, Hyloderm (1% soln. of Na hyaluronate) 5, and Polyox 1% soln. 5% by wt., had the appearance of a homogeneous viscous liq., and it gave a soft, silky feel when applied to the skin.

IT 105524-26-3
 RL: BIOL (Biological study)
 (as cosmetic and pharmaceutical gel network for water-insol. substances)

RN 105524-26-3 HCPLUS
 CN Hyaluronic acid, sodium salt, polymer with heparin and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 9067-32-7
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

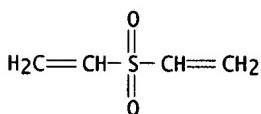
CM 2

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

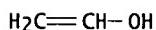
CM 3

CRN 77-77-0
 CMF C4 H6 O2 S



L47 ANSWER 44 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1986:485134 HCPLUS
 DOCUMENT NUMBER: 105:85134
 TITLE: Coating of two polyether-polyurethanes and
 polyethylene with a heparin-poly(vinyl alcohol) hydrogel
 AUTHOR(S): Evangelista, Ramon A.; Sefton, Michael V.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
 ON, M5S 1A4, Can.
 SOURCE: Biomaterials (1986), 7(3), 206-11
 CODEN: BIMADU; ISSN: 0142-9612
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Two polyether-polyurethane elastomers (Pellethane and Biomer) and
 polyethylene [9002-88-4] were coated with a heparin-poly(vinyl alc.)
 hydrogel. The requisite surface modification in prepn. for coating
 consisted of glow discharge cleaning and acid treatment for the
 polyether-polyurethanes and glow discharge cleaning and chromic acid
 oxidn. for polyethylene. The chem. modifications increased surface
 wettability. Surface anal. by attenuated total reflectance Fourier
 transform IR spectroscopy indicated that the acid treatment caused
 hydrolysis of the polyether segments of Pellethane and Biomer. Prolonged
 partial thromboplastin times were obsd. on the coated films. The results
 of Toluidine Blue assay of heparin in the soln. in which the coated films
 were immersed for a long time suggested that heparin was covalently bound
 in the coating. Such coating techniques extend the usefulness of the
 heparin-poly(vinyl alc.) hydrogel to a no. of medically important
 substrate materials.
 IT 9002-89-5D, reaction products with heparin
 9005-49-6D, reaction products with polyvinyl alc.
 RL: BIOL (Biological study)
 (coating of polyethylene and polyether-urethane rubber with,
 for biomaterials)
 RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 45 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1985:172602 HCPLUS
 DOCUMENT NUMBER: 102:172602
 TITLE: Parallel flow arteriovenous shunt for the ex vivo
 evaluation of heparinized materials
 AUTHOR(S): Ip, Wan Fong; Zingg, Walter; Sefton, Michael V.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
 ON, M5S 1A4, Can.

SOURCE: Journal of Biomedical Materials Research (1985), 19(2), 161-78
 CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The patency of heparin-poly(vinyl alc.) (hep-PVA)-coated polyethylene tubing was longer than control tubes coated with poly(vinyl alc.) but without heparin at low flow rates in dogs using a novel parallel flow arteriovenous shunt designed to avoid surgical artifacts. A std. Silastic chronic shunt (3.18 mm internal diam., (i.d.)) was inserted between the iliac artery and vein of a dog. After a 2-wk recovery period, a small diam. coated polyethylene tube (1.14 mm i.d.) was connected in parallel with the exteriorized portion of the chronic shunt through a pair of Silastic Y-connectors, so that <3% of the shunt flow was diverted into the test tube. The chronic shunt was reused many times over a >6 mo patency period, eliminating the need for frequent surgery and reducing interanimal variability in the results. The difference in patency between heparinized and control tubes was greater at higher mainshunt flow rates indicating the presence of a significant effect of the Y-connectors on platelet adhesion or aggregation. This effect was manifested in a time-dependent redn. in circulating platelet count. SEM examn. of the midportion of the heparinized tubes after occlusion demonstrated the absence of platelet and fibrin deposits, unlike the control tubes without heparin. Although the Y-connectors played a significant role, they did not dominate the thrombotic processes occurring in this shunt and consequently the biol. effectiveness of the immobilized heparin could be demonstrated.

IT 9002-89-5

RL: BIOL (Biological study)
 (heparinized polyethylene tubing coated with,
 thromboresistance of, parallel flow arteriovenous shunt for evaluation
 of)

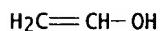
RN 9002-89-5 HCPLUS

CN Etheno1, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O



IT 9005-49-6, biological studies

RL: BIOL (Biological study)
 (poly(vinyl alc.)-coated polyethylene tubing contg.,
 thromboresistance of, parallel flow arteriovenous shunt for evaluation
 of)

RN 9005-49-6 HCPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 46 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1983:510715 HCPLUS

DOCUMENT NUMBER: 99:110715

TITLE: Preparation of heparinized biomaterials

AUTHOR(S): Evangelista, Ramon; Sefton, Michael V.

CORPORATE SOURCE: Dep: Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, MSS 1A4, Can.

SOURCE: Proc. IUPAC, I. U. P. A. C., Macromol. Symp., 28th (1982), 357. Int. Union Pure Appl. Chem.: Oxford, UK.

CODEN: 50DXAF

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Nonthrombogenic materials were obtained by coating Pellethane, Biomer, polyethylene [9002-88-4] and Cuprophane with a heparin-poly(vinyl alc.) hydrogel. The surfaces of these polymers became more wettable after initial chem. treatment and showed good adhesion to the hydrogel. The partial thromboplastin times, measured on washed and coated polymers, confirmed that the heparinized films showed some thromboresistance. Thus, the heparinized materials are potentially useful for long-term implants.

IT 9002-89-5D, reaction products with heparin
 9005-49-6D, reaction products with poly(vinyl alc.)
 RL: BIOL (Biological study)
 (polymers coated with, as biomaterials)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 47 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1983:132381 HCPLUS
 DOCUMENT NUMBER: 98:132381
 TITLE: Production of antithrombogenic regenerated cellulose membranes
 PATENT ASSIGNEE(S): Agency of Industrial Sciences and Technology, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57162701	A2	19821006	JP 1981-46286	19810331 <--
JP 59041647	B4	19841008		

PRIORITY APPLN. INFO.: JP 1981-46286 19810331
 AB Antithrombogenic membranes for hemodialysis are prep'd. by treating acrylic polymer-grafted cellulose membranes with heparin, since the grafted celluloses adsorbed more heparin than celluloses themselves. Thus, a cuprammonium cellulose film (diam. 60 mm, 15 .mu.m thick, 0.45 g) was treated with an aq. soln. contg. glycidyl methacrylate, N-vinylpyrrolidone, and cerium ammonium nitrate to obtain a polymer-grafted cellulose, which was isolated, subsequently treated with heparin, and washed with water. The antithrombogenic activity of this film was tested.

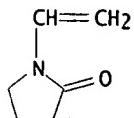
IT 9005-49-6D, reaction products with vinyl polymers and cellulose
 RL: BIOL (Biological study)
 (antithrombogenic dialysis membrane contg.)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 88-12-0D, polymers with celluloses and glycidyl methacrylate, reaction products with heparin
 RL: BIOL (Biological study)
 (graft, antithrombogenic dialysis membrane from)

RN 88-12-0 HCAPLUS
 CN 2-Pyrrolidinone, 1-ethenyl- (9CI) (CA INDEX NAME)



L47 ANSWER 48 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1982:461069 HCAPLUS
 DOCUMENT NUMBER: 97:61069
 TITLE: Nonthrombogenic polymers for artificial organs
 PATENT ASSIGNEE(S): Nitto Electric Industrial Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57075655	A2	19820512	JP 1980-153628	19801030 <--
JP 61006662	B4	19860228		

PRIORITY APPLN. INFO.: JP 1980-153628 19801030

AB Immobilization of heparin, antithrombin III, and fibrinolysis-activating enzymes on the surface of ethylene-vinyl alc. copolymer gives nonthrombogenic materials that can be used for the prepn. of artificial organs and catheters. Thus, 1 g ethylene-vinyl alc. copolymer was suspended in 5 mL 0.1M NaHCO₃, and 50 mg heparin, 10 mg antithrombin III, and 10 mg urokinase [9039-53-6], dissolved in 10 mL 0.1M NaHCO₃, were added at 4.degree.. The copolymer immobilized 50 .mu.g heparin, 130 .mu.g antithrombin, and 100 .mu.g urokinase.

IT 25067-34-9DP, reaction products with antithrombin III and heparin and urokinase
 RL: PREP (Preparation)
 (prepn. of, for nonthrombogenic material)

RN 25067-34-9 HCAPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

H₂C=CH-OH

CM 2

CRN 74-85-1
 CMF C2 H4

H₂C=CH₂

IT 9005-49-6DP; reaction products with ethylene-vinyl alc.
 copolymer
 RL: PREP (Preparation)

(prep. of, for nonthrombogenic material)
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 49 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:187142 HCPLUS
 DOCUMENT NUMBER: 96:187142
 TITLE: The esterification reaction of heparin with succinic anhydride and styrene-maleic anhydride copolymer
 AUTHOR(S): Ishikawa, Yoichiro; Yamamura, Seijiro; Yoshida, Matayasu
 CORPORATE SOURCE: Osaka Ind. Res. Inst., Osaka, Japan
 SOURCE: Osaka Kogyo Gijutsu Shikensho Kiho (1981), 32(4), 227-31
 CODEN: OKGKAE; ISSN: 0472-142X
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese

AB The esterification of heparin [9005-49-6] with succinic anhydride [108-30-5] or styrene-maleic anhydride copolymer (I) [9011-13-6] was examd. for prep. heparinized materials in which the heparin not labile. The former reaction proceeded at 45.degree. in the presence or absence of a catalyst. However, at 55-65.degree., desulfation and amide formation also occurred on the amino sulfate group in heparin. The antithrombogenic activity of heparin-succinate Na salt [81544-32-3] was slightly lower than that of original heparin. Heparinized I formed a film from a THF soln. if the heparin benzylidemethylcetylammonium salt [81507-11-1]/I ratio was <0.15, but if the ratio >0.15, gelation occurred.

IT 81544-20-9P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prep. of, nonthrombogenic biomedical polymers in relation to)
 RN 81544-20-9 HCPLUS
 CN 2,5-Furandione, polymer with ethenylbenzene, ester with heparin (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

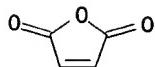
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 9011-13-6
 CMF (C8 H8 . C4 H2 O3)x
 CCI PMS

CM 3

CRN 108-31-6
 CMF C4 H2 O3



CM 4

CRN 100-42-5
 CMF C8 H8

H2C=CH-Ph

L47 ANSWER 50 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:40964 HCPLUS
 DOCUMENT NUMBER: 96:40964
 TITLE: Prosthetic materials treated with anticoagulants
 PATENT ASSIGNEE(S): Nitto Electric Industrial Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 56136564	A2	19811024	JP 1980-39927	19800327 <-- JP 1980-39927 19800327

PRIORITY APPLN. INFO.: AB Prosthetic materials contg. heparin [9005-49-6] and antithrombin III [9000-94-6] incorporated into an ethylene-vinyl alc. copolymer [25067-34-9] prevent blood coagulation when used in artificial lungs and kidneys. For example, 1-50 .mu.g heparin and 1-50 .mu.g antithrombin/cm² were immobilized on the surface of an ethylene-vinyl alc. copolymer contg. 10-50 mol% ethylene.
 IT 9005-49-6, biological studies
 RL: BIOL (Biological study)
 (ethylene-vinyl alc. copolymer contg. antithrombin III and, for artificial kidney and lung)
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 IT 25067-34-9D, reaction products with antithrombin III and heparin
 RL: BIOL (Biological study)
 (for artificial kidney and lung, blood coagulation prevention in relation to)
 RN 25067-34-9 HCPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

H2C=CH-OH

GM 2

CRN 74-85-1
 CMF C2 H4

H2C=CH2

L47 ANSWER 51 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1981:575749 HCPLUS

DOCUMENT NUMBER: 95:175749
 TITLE: Irreversible immobilization of heparin for biomaterials
 AUTHOR(S): Sefton, Michael V.; Goosen, Mattheus F. A.
 CORPORATE SOURCE: Dép. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.
 SOURCE: Developments in Biochemistry (1981), 12(Chem. Biol. Heparin), 463-74
 CODEN: DEBIDR; ISSN: 0165-1714
 DOCUMENT TYPE: Journal
 LANGUAGE: English.

AB The effectiveness of heparin [9005-49-6] irreversibly bound to a polymer substrate was demonstrated by both in vitro and ex vivo assays. Heparin was bound to poly(vinyl alc.) (PVA) through an acetal bridge by reaction of heparin, PVA and a mixt. of aldehydes at 70-80.degree.. The resulting gel was ground to form small beads or was applied to the hydroxylated surface of a styrene-butadiene-styrene block copolymer (SBS). The elution rate of 35S-heparin from the surface was < the detection limit (i.e., < 10⁻⁴ .mu.g/cm²min) after 60 h of washing in phosphate buffers. Nevertheless, the partial thromboplastin time of plasma incubated in tubes made from heparinized SBS was significantly greater (> 1200 s) than that with the control (120 s). Furthermore the recalcification time of plasma incubated with gel beads was prolonged in direct correlation with the amt. of gel added to the plasma. Ex vivo assays were more complex, however. At high shear rates platelet adhesion dominated with no difference being exhibited by heparinized tubing and control tubing with a PVA coating but without heparin. At very low shear rates, however, the heparinized shunt remained patent for 6 days. Exposure of a column of PVA-heparin beads to both thrombin [9002-04-4] and antithrombin [9000-94-6] III in various sequences demonstrated that thrombin binding to heparin is a primary stage in thrombin inactivation. Only when thrombin was loaded before antithrombin III was there significant inactivation of the bound thrombin. Thus it appears that despite the absence of significant heparin elution, bound heparin retains at least part of its biol. activity. Bound heparin appears to act in like manner to dissolved heparin to promote thrombin-antithrombin III complex formation.

IT 9002-89-5D, reaction products with heparin
 RL: BIOL (Biological study)
 (butadiene-styrene copolymer bound, for vascular prosthetics)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

H₂C=CH-OH

IT 9005-49-6, properties
 RL: PRP (Properties)
 (immobilized on poly(vinyl alc.) and bound to hydroxylated butadiene-styrene copolymer surface, for vascular prosthetics)
 RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 52 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1981:521112 HCPLUS
 DOCUMENT NUMBER: 95:121112
 TITLE: Patency of heparinized SBS shunts at high shear rates
 AUTHOR(S): Sefton, Michael V.; Zingg, Walter
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,

SOURCE: ON, M5S 1A4, Can.
 Biomaterials, Medical Devices, and Artificial Organs (1981), 9(2), 127-42
 CODEN: BMDOAI; ISSN: 0090-5488

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The patency of 50 cm long, 1.7 mm (internal diam.) heparin [9005-49-6]-poly(vinyl alc.) (PVA) [9002-89-5] coated Kraton rubber 1102 (SBS) arteriovenous shunts in pigs at shear rates >1000/s was not different from that of identical shunts coated with PVA but without heparin. This was attributed to the absence of any measurable effect of surface bound heparin on platelet related thrombus formation at high shear rates. On the other hand, platelet adhesion values detd. in the absence of flow by the open static method decreased with increasing heparin content in heparin-PVA films. The low overall patency (av. life of 170 min) of the PVA coated SBS shunts (with and without heparin) was related to the absence of circulating heparin during surgery and the consequent presence of tissue thromboplastin or cellular debris during the immediate postoperative period. Alternative protocols are needed to test heparinized materials at low shear rates in the absence of systemic heparin to properly assess the potential thromboresistance of such materials.

IT 9005-49-6, biological studies
 RL: BIOL (Biological study)
 (SBR rubber coated with poly(vinyl alc.) and, patency of, at high shear rates)

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

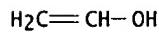
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-89-5
 RL: BIOL (Biological study)
 (SBR rubber shunts coated with heparin and, patency of, at high shear rates)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O



L47 ANSWER 53 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1979:409461 HCPLUS
 DOCUMENT NUMBER: 91:9461
 TITLE: Heparinized styrene-butadiene-styrene elastomers
 AUTHOR(S): Goosen, Mattheus F. A.; Sefton, Michael V.
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.
 SOURCE: Journal of Biomedical Materials Research (1979), 13(3), 347-64
 CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A surface hydroxylated styrene-butadiene-styrene block copolymer (I) was coated with acetylated polyvinyl alc.-heparin (II) mixt. contg. glutaraldehyde and MgCl₂, and then cured at 80.degree. for 100 min to give heparinized elastomer in which polyvinyl alc. hydroxylated I, and II were covalently bound to each other by acetal bridges. II was not leached from the surface of the elastomer with 3M saline at pH 7.4. The heparinized

elastomer is potentially useful as a nonthrombogenic vascular prosthetic. Preliminary ex vivo testing, using an arteriovenous shunt, showed good thromboresistance; the shunt remained free of thrombi for >2 h, without desorption of II while the control remained patent for <15 min.

IT 9002-89-5D, reaction products with heparin and aldehydes and hydroxylated butadiene-styrene rubber 9005-49-6D, reaction products with poly(vinyl alc.) and aldehydes and hydroxylated butadiene-styrene rubber
 RL: BIOL (Biological study)
 (for nonthrombogenic vascular prosthesis)

RN 9002-89-5 HCPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

RN 9005-49-6 HCPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

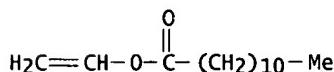
L47 ANSWER 54 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1978:547260 HCPLUS
 DOCUMENT NUMBER: 89:147260
 TITLE: Heparin derivatives of high molecular weight
 AUTHOR(S): Mester, L.; Amit Amaya, A.; Mester, M.
 CORPORATE SOURCE: Inst. Chim. Subst. Nat., CNRS, Gif-sur-Yvette, Fr.
 SOURCE: ACS Symposium Series (1978), 77(Carbohydr. Sulfates), 113-20
 CODEN: ACSMC8; ISSN: 0097-6156

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Polymn. of heparin methacrylate (I) [67712-81-6] with AIBN in dioxane gave sol. or gelatinous polymer [67770-19-8], depending on the d.p. Polymn. of I with alkyl methacrylates or vinyl compds. gave fat-sol. polymers with a higher d.p. Polymn. with crosslinking agents such as divinylbenzene or N,N'-methylenebis(acrylamide) gave polymers with completely altered mol. geometries. Structural changes in I polymer and I-Bu methacrylate copolymer [67800-50-4] were detd. by CD. The antithrombic activity of some of the high-mol. wt. polymers decreased, while the antilipemic activity increased considerably or was unchanged. The insol. polymers could be used for coating surfaces.

IT 67784-40-1P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prep., properties and biol. activity of)
 RN 67784-40-1 HCPLUS
 CN Heparin, 2-methyl-2-propenoate, polymer with ethenyl dodecanoate (9CI) (CA INDEX NAME)

CM 1

CRN 2146-71-6
 CMF C14 H26 O2

CM 2

CRN 67712-81-6
 CMF C4 H6 O2 . x Unspecified

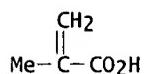
CM 3

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 79-41-4
 CMF C4 H6 O2



IT 67770-18-7
 RL: USES (Uses)
 (structural geometry of)
 RN 67770-18-7 HCPLUS
 CN Heparin, 2-methyl-2-propenoate, polymer with diethenylbenzene (9CI) (CA INDEX NAME)

CM 1

CRN 1321-74-0
 CMF C10 H10
 CCI IDS



2 [D1-CH=CH2]

CM 2

CRN 67712-81-6
 CMF C4 H6 O2 . x Unspecified

CM 3

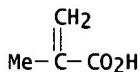
CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

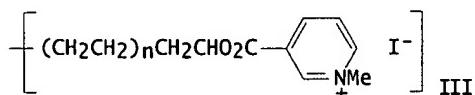
CRN 79-41-4

CMF C4 H6 O2



L47 ANSWER 55 OF 55 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1978:517856 HCPLUS
 DOCUMENT NUMBER: 89:117856
 TITLE: Polymers containing amine groups and quaternary ammonium groups existing free or in salt form
 INVENTOR(S): Serboli, Giancarlo; Straziota, Maurizio; La Barba, Nicolina
 PATENT ASSIGNEE(S): Anic S.p.A., Italy
 SOURCE: Ger. Offen., 15 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2750542	A1	19780518	DE 1977-2750542	19771111 <--
CA 1092287	A1	19801223	CA 1977-289018	19771019 <--
IL 53214	A1	19820430	IL 1977-53214	19771025 <--
US 4182804	A	19800108	US 1977-847426	19771101 <--
ZA 7706556	A	19780830	ZA 1977-6556	19771103 <--
FR 2370759	A1	19780609	FR 1977-33452	19771107 <--
FR 2370759	B1	19801024		
CH 628656	A	19820315	CH 1977-13541	19771107 <--
DK 7704957	A	19780512	DK 1977-4957	19771108 <--
GB 1584078	A	19810204	GB 1977-46446	19771108 <--
SE 7712687	A	19780512	SE 1977-12687	19771109 <--
NO 7703835	A	19780512	NO 1977-3835	19771109 <--
JP 53060988	A2	19780531	JP 1977-133675	19771109 <--
BE 860735	A1	19780510	BE 1977-182557	19771110 <--
NL 7712409	A	19780516	NL 1977-12409	19771110 <--
PRIORITY APPLN. INFO.:		IT 1976-29235		19761111
GI				

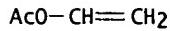


- AB The title polymers were prep'd. by hydrolyzing an ethylene-vinyl acetate copolymer, contg. 26.5% vinyl acetate, to give a vinyl alc. copolymer $-\text{(CH}_2\text{CH}_2)_n\text{(CH}_2\text{CHOH})_m-$ (I), which was acylated with $\text{ClCH}_2\text{CO}_2\text{H}$ and heated with HNET_2 to give $-\text{(CH}_2\text{CH}_2)_n\text{(CH}_2\text{CHO}_2\text{CCH}_2\text{NEt}_2)_m-$ (II). II was quaternized with undecylenic acid, and the product adsorbed on gauze for use in the treatment of mycosis. II, quaternized with sorbic acid, and used to treat the inside of fruit juice containers, improved the stability of the juices. A II film was treated with Na heparinate to give a surface heparin concn. of 0.06 mg/cm². I was also acylated with nicotinoyl chloride-HCl and quaternized with MeI to give III.
- IT 24937-78-8D, hydrolyzed, esters with quaternary ammonium carboxylates
 RL: BIOL (Biological study)
 (as nonthrombogenic materials)

RN 24937-78-8 HCPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

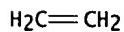
CM 1

CRN 108-05-4
 CMF C4 H6 O2



CM 2

CRN 74-85-1
 CMF C2 H4



IT 9041-08-1
 RL: BIOL (Biological study)
 (quaternized amino ethylene-vinyl acetate copolymers
 treatment with, as nonthrombogenic materials)
 RN 9041-08-1 HCPLUS
 CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d cost COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
CONNECT CHARGES	77.33	93.27
NETWORK CHARGES	4.81	7.69
SEARCH CHARGES	0.00	109.66
DISPLAY CHARGES	247.55	259.14
<hr/>		
CAPLUS FEE (5%)	329.69	469.76
<hr/>		
FULL ESTIMATED COST	16.24	17.13
<hr/>		
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-35.81	-37.11

IN FILE 'HCPLUS' AT 16:08:57 ON 03 SEP 2003

=> log hold COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	345.93	486.89
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-35.81	-37.11

SESSION WILL BE HELD FOR 60 MINUTES
 STN INTERNATIONAL SESSION SUSPENDED AT 16:09:12 ON 03 SEP 2003

Host Name:
 OK

KRISHNAN 09/937,991

Q!5ATHZ
OK

Inventor search

KRISHNAN 09/937,991

> d que

L1 8544 SEA FILE=HCAPLUS ABB=ON PLU=ON SAITO Y?/AU
 L2 2083 SEA FILE=HCAPLUS ABB=ON PLU=ON ISHIHARA M?/AU
 L3 4755 SEA FILE=HCAPLUS ABB=ON PLU=ON ONO K?/AU
 L4 4669 SEA FILE=HCAPLUS ABB=ON PLU=ON ISHIKAWA K?/AU
 L5 19976 SEA FILE=HCAPLUS ABB=ON PLU=ON (L1 OR L2 OR L3 OR L4)
 L6 32 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND GLYCOSAMIN?
 L7 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND POLYMER?
 L8 10 SEA FILE=REGISTRY ABB=ON PLU=ON (106096-93-9/B1 OR 127464-60-
 2/B1 OR 24967-94-0/B1 OR 25322-46-7/B1 OR 154531-34-7/B1 OR
 83869-56-1/B1 OR 9003-53-6/B1 OR 9005-49-6/B1 OR 9041-08-1/B1
 OR 9050-30-0/B1)
 L9 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND L7

> d ibib abs hitstr ind 1-2

(# 3 was not relevant)

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:793739 HCAPLUS
 DOCUMENT NUMBER: 137:284439
 TITLE: Glycosaminoglycan functional polymer
 and adhesion protein complexes and applications
 thereof
 INVENTOR(S): Yura, Hiroyumi; Ishihara, Masayuki;
 Saito, Yoshio; Ono, Katsuaki; Sato,
 Masato
 PATENT ASSIGNEE(S): Netech Inc., Japan
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081619	A1	20021017	WO 2002-JP3287	20020402
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: JP 2001-102883 A 20010402
 AB It is intended to construct environment similar to an extracellular matrix by combining a glycosaminoglycan (GAG) functional polymer with a cell adhesion protein such as collagen, and the GAG functional polymer/protein complexes characterized in that the GAG functional polymer, which has a sugar chain contg. a structure corresponding to at least a part of the basic skeleton of GAG introduced into the main chain of a vinyl-type polymer, is carried on a cell adhesive protein; differentiation and proliferation of cells can be controlled in the novel material and the complexes can be used as cell culture materials and tissue regeneration materials. Heparin-carrying polystyrene (HCPS) was prep'd. The HCPS efficiently bound to collagen-coated cell culture plate, thereby retaining the binding of vascular endothelial growth factor (VEGF)165 or fibroblast growth factor (FGF)-2. Human umbilical vein endothelial cells showed a good adherence to the HCPS-bound collagen substrate.
 IT 83869-56-1, GM-CSF 106096-93-9, FGF-2
 127464-60-2, Vascular endothelial growth factor
 154531-34-7
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(glycosaminoglycan-carrying vinyl polymers binding
with proteins and growth factor or cytokines for cell adhesion)

RN 83869-56-1 HCPLUS
CN Colony-stimulating factor 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 106096-93-9 HCPLUS
CN Fibroblast growth factor, basic (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 127464-60-2 HCPLUS
CN Vascular endothelial growth factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 154531-34-7 HCPLUS
CN Epidermal growth factor-like growth factor, heparin-binding (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

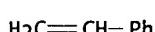
IT 9003-53-6DP, Polystyrene, reaction products with
glycosaminoglycans 9005-49-6DP, Heparin, reaction
products with polystyrene 25322-46-7DP, Chondroitin sulfate C,
reaction products with polystyrene
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)
(glycosaminoglycan-carrying vinyl polymers binding
with proteins for cell adhesion)

RN 9003-53-6 HCPLUS
CN Benzene, ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 100-42-5

CMF C8 H8



RN 9005-49-6 HCPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-46-7 HCPLUS
CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

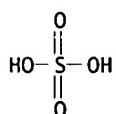
CM 1

CRN 9007-27-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
CMF H2 O4 S



IT 9050-30-0D, Heparan sulfate, reaction products with vinyl polymers 24967-94-0D, Dermatan sulfate, reaction products with vinyl polymers
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with proteins for cell adhesion)

RN 9050-30-0 HCPLUS
 CN Heparan, sulfate (9CI) (CA INDEX NAME)

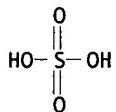
CM 1

CRN 70226-44-7
 CMF Unspecified
 CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



RN 24967-94-0 HCPLUS
 CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

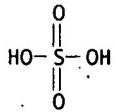
CM 1

CRN 75634-40-1
 CMF Unspecified
 CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



IC ICM C12M003-00
 ICS C08H001-00; A61K031-726; A61K031-727; A61K038-22; A61K047-42;
 A61P043-00; A61L027-00
 CC 63-7 (Pharmaceuticals)
 ST glycosaminoglycan polymer protein cell adhesion
 IT Cytokines
 Growth factors, animal
 Hepatocyte growth factor
 Interleukin 3
 Transforming growth factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with proteins and growth factor or cytokines for cell adhesion)

- IT Adhesion, biological
 Animal tissue culture
 Cartilage
 Human
 Regeneration, animal
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)
- IT Collagens, biological studies
 Proteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)
- IT Vinyl compounds, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (polymers; glycosaminoglycan-carrying vinyl
 polymers binding with proteins for cell adhesion)
- IT Glycosaminoglycans, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (reaction products with vinyl polymers;
 glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)
- IT Vein
 (umbilical, endothelium; glycosaminoglycan-carrying vinyl
 polymers binding with proteins for cell adhesion)
- IT 83869-56-1, GM-CSF 106096-93-9, FGF-2
 127464-60-2, Vascular endothelial growth factor
 154531-34-7
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins and growth factor or cytokines for cell adhesion)
- IT 9003-53-6DP, Polystyrene, reaction products with
 glycosaminoglycans 9005-49-6DP, Heparin, reaction
 products with polystyrene 25322-46-7DP, Chondroitin sulfate C,
 reaction products with polystyrene
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)
- IT 9050-30-0D, Heparan sulfate, reaction products with viny
 polymers 24967-94-0D, Dermatan sulfate, reaction
 products with viny polymers
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)
- REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 HCPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:725687 HCPLUS
 DOCUMENT NUMBER: 133:305617
 TITLE: Functionalized glycosaminoglycan
 polymer and medical instruments and drugs by
 using the same
 INVENTOR(S): Yura, Hirofumi; Saito, Yoshio;
 Ishihara, Masayuki; Ono, Katsuaki;
 Ishikawa, Keiichi
 PATENT ASSIGNEE(S): Netech Inc., Japan
 SOURCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	-----	-----	-----	-----
WO 2000059967	A1	20001012	WO 2000-JP2012	20000330

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1172386 A1 20020116 EP 2000-912966 20000330

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: JP 1999-97062 A 19990402
WO 2000-JP2012 W 20000330

AB Functionalized polymers widely usable in the fields of drugs and medical instruments which are obtained by functionalizing, by org. synthesis, glycosaminoglycan controlling the adhesion, migration and proliferation of cells via binding to various cell growth factors and cytokines or direct interactions with cells. These functionalized polymers are characterized by having a sugar chain involving a structure corresponding to at least a part of the fundamental glycosaminoglycan skeleton introduced into the main chain of a vinyl polymer.

IT 106096-93-9, FGF 2 127464-60-2, Vascular endothelial growth factor

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(functionalized glycosaminoglycan polymer and medical instruments and drugs by using the same)

RN 106096-93-9 HCPLUS

CN Fibroblast growth factor, basic (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 127464-60-2 HCPLUS

CN Vascular endothelial growth factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9041-08-1, Sodium heparin 24967-94-0, Dermatan sulfate 25322-46-7, Chondroitin sulfate c

RL: RCT (Reactant); RACT (Reactant or reagent)
(functionalized glycosaminoglycan polymer and medical instruments and drugs by using the same)

RN 9041-08-1 HCPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24967-94-0 HCPLUS

CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

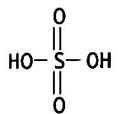
CM 1

CRN 75634-40-1
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
CMF H2 O4 S



RN 25322-46-7 HCPLUS
 CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

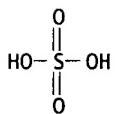
CM 1

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



IC ICM C08F246-00
 ICS C08F008-00; C08B037-00; A61K031-785; A61P035-00; G01N033-48;
 C12M003-00; A61L002-16

CC 1-12 (Pharmacology)

Section cross-reference(s): 2, 15, 63

ST glycosaminoglycan polymer medical good drug

IT Adhesion, biological

Antitumor agents

Medical goods

Proliferation inhibition

(functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)

IT Glycosaminoglycans, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)

IT Biopolymers

Cytokines

Growth factors, animal

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)

IT Growth factors, animal

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(heparin-binding; functionalized glyc saminoglycan
 polymer and medical instruments and drugs by using the same)

IT Mucopolysaccharides, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)

(heparinoids; functionalized glyc saminoglycan
polymer and medical instruments and drugs by using the same)

IT Vinyl compounds, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)

(polymers; functionalized glycosaminoglycan
polymer and medical instruments and drugs by using the same)

IT 106096-93-9, FGF 2 127464-60-2, Vascular endothelial
growth factor

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)

(functionalized glycosaminoglycan polymer and
medical instruments and drugs by using the same)

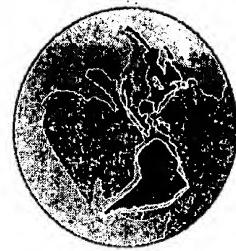
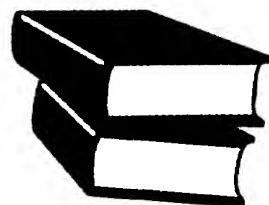
IT 9041-08-1, Sodium heparin 24967-94-0, Dermatan sulfate

25322-46-7, Chondroitin sulfate c

RL: RCT (Reactant); RACT (Reactant or reagent)

(functionalized glycosaminoglycan polymer and
medical instruments and drugs by using the same)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



Foreign Patents & Scientific Literature Branch
Examiner Document Request Form FY 2003

Last Name: KRISHNAN First Name _____

Date Assigned: 08-26-2002

TechCenter 1623 Date Completed: _____

Phone: 305-4837

Case Number: _____

Country JP Patent No. 510783 Pages Tech Center
Country _____ Patent No. _____ Pages Tech Center

Country _____ Patent No. _____ Pages Tech Center
Country _____ Patent No. _____ Pages Tech Center

Country _____ Patent No. _____ Pages Tech Center

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Country _____ Patent No. _____ Pages Tech Center

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Country _____ Patent No. _____ Pages Tech Center

Country _____ Patent No. _____ Pages Tech Center

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U.S. PAT. & TM. OFFICE

(19)日本国特許庁 (JP)

(12) 公表特許公報 (A)

(11)特許出願公表番号

特表平6-510783

第3部門第2区分

(43)公表日 平成6年(1994)12月1日

(51) Int.Cl.*	識別記号	序内登録番号	F 1
A 61 K 47/48	Z	7433-4C	
C 08 B 37/08	A	7433-4C	
I A 61 K 31/725		9454-4C	
31/73		9454-4C	
31/785		9454-4C	

審査請求 未請求 予審査請求 有 (全 11 頁) 最終頁に続く

(21)出願番号 特願平5-505996
 (36) (22)出願日 平成4年(1992)9月25日
 (35)翻訳文提出日 平成6年(1994)3月25日
 (36)国際出願番号 PCT/SE92/00672
 (37)国際公開番号 WO93/05793
 (87)国際公開日 平成5年(1993)4月1日
 (31)優先権主張番号 9102798-7
 (32)優先日 1991年9月26日
 (33)優先権主張国 スウェーデン(SE)
 (35)指定国 EP(AT, BE, CH, DE,
 DK, ES, FR, GB, GR, IE, IT, LU, M
 C, NL, SE), AU, CA, JP, US

(71)出願人 コルリーネ・システムズ・アクチエボラーグ
 スウェーデン国エス-750 68 ウブサラ.
 ボンクス8037
 (72)発明者 ラーソン, ロルフ
 スウェーデン国エス-750 52 ウブサラ.
 ブルームステル ヴエイエン19
 (72)発明者 ヴエストベルイ, ダーヴィット
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(54)【発明の名称】 新規接合体、その調製および使用ならびにその接合体を用いて調製された基体

(57)【要約】

本発明は、多数の官能基をポリマー主鎖に沿って分布させた実質的に鎖状の有機ポリマーであって、それら官能基を介してその非活性部分中の硫酸化グリコサミノグリカン類群からの多数の分子が共有結合を通して結合されているものよりなる実質的に水溶性の生物学的に活性な接合体に関する。また本発明は接合体の製造、接合体を用いた基体表面の潤滑、このようにして調製された基体表面および治療剤として用いるための接合体にも関する。

記念の鳥

1. 多数の官能基をポリマー主鎖に沿って分布させた炎属性に優れた
の有機ポリマーであって、それらは溶液を介してその炎属性部分
の強化性グリコサミノグリカン群から少なくとも約20分子が
共有結合を経て結合されているものより成る実質的に水溶性の
生物学的に活性な複合体。
 2. 島状ポリマーが天然または合成のオリペチド、多糖体または
脂肪族ポリマーに由来する精次第¹記載の複合体。
 3. 島状ポリマーの架橋がアリシン、ポリオルニチン、キトサン、ガ
リイミンまたはポリアリルアミン由来する酵素項²記載の複合
体。
 4. グリコサミノグリカン類が実質的に単結合を介して、好ましく
は末端でポリマー主鎖に結合している酵素項¹、2または3胚
體の複合体。
 5. グリコサミノグリカン類が単グリコサミノグリカン類に結合し
たアミノ基を介したポリマー主鎖に結合されている酵素項¹～4
のいずれかに記載の複合体。
 6. 複合体がそのグリコサミノグリカン類の性に、水に溶解され
た場合に実質的にその会長に沿って正直性基体表面に専門的相互作
用により不規則的に結合され得るのに十分なポリマー
結合を有することを特徴とする酵素項¹～5のいずれかに記載
の複合体。
 7. 少なくとも30グリコサミノグリカン残基を有する酵素項¹～8
のいずれかに記載の複合体。
 8. 少なくとも100グリコサミノグリカン残基を有する酵素項¹～8

に複数な複合体の構成を示す。

16. 多数のセラミドをポリマー-核酸に加えて分子された質的に類似の内膜複合リマーであって、それらを核酸を介して酰化グリコサミノグリカン類細胞からの多数の分子が共有結合を通して結合されているものより改るは結合を複合体に対するアフィニティを有する基質異同と、結合がそこに質的に不可逆的に結合されるように親和させることを特徴とする、酰化グリコサミノグリカン類によく表面の調製方法。

17. 複合体がポリ陽イオン性を有し、基質表面が陽イオン性である相承水16把載の方針。

18. 基質側として用いるための清承水11-12のいずれかに記載の生物学的に活性な複合体。

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敵の操作体。

9. 前記グリコサミノグリカンがペルリンまたはその削片または接着体である結果項3～8のいずれかに記載の場合は、

10. グリコサミノグリカン残基が結合強度を介してポリマー主鎖に結合される結果項3～9のいずれかに記載の場合は、

11. 前記各判定がヘテニ-二重的結合結果由来する請求項10記載の場合は、

12. ポリマー主鎖がグリコサミノグリカン類のほかに少なくとも一つの付加的に生物学的に活性な物質の残基を抱有する結果項3～11のいずれかに記載の場合は、

13. 組合体が多数の官能基をポリマー主鎖に抱って分離させた実験的に直鎖状の直鎖ポリマーであって、それら官能基を介して酸触化グリコサミノグリカン残基からの多数の分子が交叉結合を通して結合されているものより成り、該組合体は好ましくは該組合体と赤外吸収との間の電離的相互作用により表面に結合されていることを特徴とする、妥協にアフィニティ結合された生物学的に活性な結合様式による成る調製された基体表面。

14. 生物学的に活性な結合体が請求項3～11のいずれかに記載の場合は、

15. 多数の官能基をポリマー主鎖に抱って分離させた実験的に直鎖状の直鎖ポリマーを有し、そしてこれら官能基に、所望により結合剤を介して、その赤外吸収部分の酸触化グリコサミノグリカン残基からの多数の分子を交叉結合的に結合させることより成ることを特徴とする、既報アグリコサミノグリカン残基からの多数の分子を抱有する実験的に直鎖状の直鎖ポリマーにより成る生物学的に

列傳 第二十一

動植物食は、その組合および應用から既に

それを複合化を利用して強調された蒸気

す認めは、醸化グリコサミングリカンに基づく新規な生物学的に活性な結合体、その結合体の製造方法、その空間がかかる結合体を用いて再製されている基体、およびその結合体を用いた表面再製方法に関する。

硫酸化ケリコサミノグリカン類は、多くの内生硫酸化ムコ多糖、例えばヘパリン、ヘパラン醣盤、ダルマタン質質、コンドロイチン醣盤など多くの様々な生物的な化合物を有するもの日本名前である。本発明は硫酸化ケリコサミノグリカン類一般に対するものであるが、以下においては、これまで医学内に最も用いられているグリコサミングリカン、すなわちヘパリンに関する記載を示すのである。

ヘパリンは細かな吸着物質組織、例えば膜、肝臓および肺臓のほかアスト田舎地で、クンバク質に複数に粘合した形で天然に存在しものをうえ $10,000$ までに分子量を有しているが、市販の製剤物は、精製および粗略方法に応じて約 $0,000$ ～ $20,000$ の範囲で販売する分子量を有している。それは交叉に存在するグルコロン酸およびグルコサミン単位よりなり、またその抗凝血作用は抗トロンビン結合活性を有する分子の特徴の五箇所位に働きしていることが示されている。

ヘバリンは遊走ブタ網膜から西製されるが、その抗凝固作用の
上に、血液を溶解するための多分性凝血が形成を防止するための、
剤として用いられている。後者は、とりわけ網膜や血管が生体にと
って構造である各血管と接することになる他の外の筋膜系、い

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わゆる体外循環（例えば人工腎臓、人工心肺装置、酸素供給器）における患者血栓の処理を伴うような手順、例えば腫瘍患者治療、開心術および集中治療などにおける手術の場合に用いられる。

このような系における血液の凝固性を障害し、またそれによって凝固による凝固を避けるためには高濃度のヘパリンを血液に添加する必要がある。それに伴って出店の危険が実質的に高まり、またそれは最悪の場合には生命を脅かす状態を招きかねないことから過半数の、そのかわりにヘパリンを表面結合することにより血液が接触する生体にとって弱剤である物質を調査させて両者の凝固性止血作用を遮蔽させようとする努力がなされてきている。この開発を刺激した既存的要因は、ヘパリンの構造、活性部位が解明されたこと、および、ヘパリン接着性が天然の血管壁上に活性化されたことである。すなわち、この数年の間に、表面結合へパリンを備えた系による体外循環の成功に関する報告がいくつか発表されている。

しかしながら、ヘパリンによる表面活性は前述の体外循環装置に関する文献に記載されるものではなく、血液および他の生物組織と接触する医療における様々なデバイスのバイオコンバチビリティを達成するという課題に対するより一般的な解決策として明らかられるようになってきている。例えば、表面へパリン化は尿内レンズのバイオコンバチビリティを終上さるるために用いられている。

ヘパリンの固定といつては対して直接から用いられている解決策は二つの主要原理、イオン的に結合したヘパリンと共有結合的に結合したヘパリンに分けることができるところ、これを以下序筋する。固定化へパリンに基づく表面のバイオコンバチビリティを示す表面を得るにはヘパリンがその生物学的活性が保たれるように開発しないということを図示しているかもしれない。

①. 共有結合的に結合したヘパリン

純化学的見地からは共有結合によるヘパリン固定化方法には多くの種々なものがある。しかしながら、共化シアン、カルボキシドおよび同様の一般的に用いられる結合技術を用いる場合には、各ヘパリン分子が活性基团中の結合を含むいくつかの結合により結合される。そのためにはヘパリンがその生物学的活性を失うという明らかな危険が伴性する。共有結合結合は最もそれ以外に、常にそれ自身有毒であり、近くで毒性を示すと誤認されるべきである。

しかしながら、US-A-4,013,665は、ヘパリンおよび他の多糖体をヘパリン分子中に含有する同一の反応性アルdehyド基を介して結合することを記載している。この場合、ヘパリンは抗トロンピン結合性配列を結合に用与せることなく共有結合的に結合されることとは可能である。しかしながら、この方法では、ヘパリンを最初に分解すること、そして表面活性であるシアノギロヒドリドを表面活性工芸に存在させることが必要となる。

EP-A-351,314は、N-硫酸化に付されたヘパリンの逆轉アミノ基を用いることによりヘパリンを逆轉アミノ基含有高分子表面に（例えばポリエチレン！）またはセトサンによる表面活性を有じ

定めることができる。導入部に記したとおり、ヘパリンの生物学的活性は特定の抗トロンピン・結合性五糖構造があり、血液の糖成分との相互作用が可能となるにはその構造が表面に固定された後も完全な形で残っていかなければならない。ヘパリンの固定化に関する大部分の学術論文および特許、特に1980より前に発表されたものは、この点で周辺のいくものはなく、また、その調整方法が完全なバイオコンバチブル表面を与えるかどうかの判断を考慮にする結果となることはさかに少ない。以下に、既知のヘパリン固定化方法を総括する。

②. イオン的に結合したヘパリン

ヘパリンは極めて多数の負荷基を含んでおり、ヘパリン分子は静電相互作用だけを通して陽イオン性表面に反応的強く結合することができる。適用される手順の一つは、ヘパリンをその水溶液から陽イオン界面活性剤で洗浄された後、乾燥化膜を有機溶媒で溶解することにより成る。後者の溶解は、次いでいわれる浸漬-dip-dry 法で用いられる。溶解速度を速めるために様々な分散界面活性剤が試験されている。その他の方法は第四級アンモニウム基へのヘパリンの吸着に基づいている。イオン的に結合したヘパリン表面が共通して持つ火炎分析の一つは、活性と接触しているヘパリンの燃焼に関する安定性が不十分な点である。

U.S.特許は、Bleasby, Med. Dev., Art. Org., 11(1983)161-173 で特に、安定なイオン的に結合した表面の調製方法を記載している。しかしながら結合型ヘパリンはその生物学的活性を失うと報告されているが、このことは、各個ヘパリン分子があまりに強固に結合されているために抗トロンピン結合性配列が血中糖類成分と相互作用し

て）結合する方法を記載している。次に多官能性アルdehyド、例えばグルタルアルアルdehyドを用いて架橋が行われる。しかしながら、グルタルアルdehyドとの反応工程は、活性配列が開裂しないよう確実にコントロールすることができず、また活性自体が、技術的観点からして、実施上相当複雑である。

US-A-4,239,664は、PPGを族ボリマーが次いでヘパリン上の水酸基と反応するイミドイルイオンを含むするように活性することにより調製されたPPG-ヘパリンポリマーを記載している。この方法は、必然的にヘパリンに対し多量の非活性的結合を有し、その生物学的活性に影響を与える。そのPPG-ヘパリンポリマーは疎水-親水性活性基を有しているとされている。

EP-A-241,895はヘパリンの如きの表面活性剤をポリ酸を介して結合したポリマー基を示している。この基体は、ポリ酸をポリマー骨格上の少數の反応性基に共有結合的に結合することによって活性可能な表面活性基の量を増加させることにより調製される。次に抗凝固剤を具体的には既にその欠点について記した既存US-A-4,013,665に記載の方法によって、ポリ酸のカルボキシルまたはアミノ基に共有結合的に結合する。

US-A-4,415,490は、ヘパリンが各結合基において唯一のアセタールまたはヘミアセタール結合を通じて各種ポリマーに結合した非活性結合材料を開示している。一方においては、アルdehyド基をセルロースなどのポリマーに導入した後、そのアルdehyド基をヘパリン中の水酸基と反応させる。このプロセスには各ヘパリン分子の複数の水酸基が関与し、またヘパリンの生物学的に活性な配列（この配列は当該特許の出版日には実施上文献に知られたり記載された

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りしていなかった)において水溶基が利用できることから、その場合は配列中の水溶基も関与し、その結果最終生成物が不活性になると明らかな危険がある。もう一つの選択法としての選択においては、代りにアルデヒド基を過ヨウ素酸処理によりヘパリンに導入する。この選択も特異性を欠き、結って結合は低級配列を含むヘパリン鎖においてランダムに生じる。

このように、以上から明らかなように表面-ヘパリン化についてこれまで知られた方法は、多かれ少なかれ既大な欠点を伴っている。結って簡便に実施でき、また低級鎖を含まずかつヘパリンの生物学的活性が保存された安全なヘパリン化製剤を求める表面-ヘパリン化方法が必要とされている。

ヘパリンの抗凝剤としての用途にもヘパリンの極限濃度および/またはアフィニティーの値は材料である。ヘパリンを抗凝剤として用いる場合だけではなく、例えば血栓溶解(溶出法)の場合の抗凝剤として、例えば慢性閉塞性(喘息)などのための呼吸器病として、および動脈形成(血管形成)薬剤としての研究された場合に用いる場合に、特にそうである。ヘパリンの総合性状の総括は "Heparin: Clinical and biological properties. Clinical applications," LaneおよびLinden 著、Edenrof Arnold. ロンドン、1980年にらることができる。結って良い事跡と増大したアフィニティーを有するヘパリン調節剤が必要とされている。

本発明によれば架橋化グリコサミノグリカン類に基づく生物学的に活性な複合体が組成され、その複合体によって架橋化グリコサミノグリカン類の性質を磨きの性質よりもはるかに効率的に利用することができる。かかる複合体はとりわけ、該複合体アフィニティー

を有する基体表面に安定期に結合させることができ、そしてそれによって例えばヘパリンの場合には、従来方法によるより簡単かつ効率的に表面-ヘパリン化を行うのに用いることができる。さらに、かかる複合体は地物質に基づく調製法よりも長い半減期および向上したアフィニティーを有するグリコサミノグリカン調節剤を与えることができる。

ヘパリンについて記述したように、架橋化グリコサミノグリカン類は天然にはタンパク質に結合した形で存在する。すなわち、例えばヘパリンの場合には、約15-ヘパリン鎖が約25アミノ酸残基のタンパク質に結合し、一方、ヘパリン硫酸を含むプロテオグリカンに架橋されたヘパリン硫酸類の方はほとんどなくはるかにまばらである。天然蛋白質は純粋な形で調製することが並めて困難であり、また我々の知る限り治療または回復の用途に付随されていない。本発明は、架橋化グリコサミノグリカンとポリマー結合との間で半または全自成結合を作るという思想に基づいている。この複合体は、とりわけ多くの分子の当該グリコサミノグリカンを含むことにより、個々のグリコサミノグリカン鎖および天然結合よりも改善された性質を有し、またさらに相対的親度を種々な用途に適するよう調節可能に変えることができるという重要な特徴を有する。

すなわち本発明はそのもと最も広い範囲において、多数の官能基をポリマー主鎖に沿って分布させた実質的に直鎖状の高分子やまたはヘテロポリマーであって、それら官能基を介してその活性部位中の架橋化グリコサミノグリカン類(GAG) 骨架の少なくとも約30分子が内包結合を通して結合されているものより成る。好ましくは、実質的に純粋な形の、少なくとも実質的に水溶性の生物学的に活性

な複合体(既大分子)を有する。

かかる複合体は既大的に合成グリコテオグリカンと交わすことができ、その相対的親度は、測定開始に及んでることができまた意図する用途に適合させることができる。

本明細書における「架橋化グリコサミノグリカン類」という表現は、その用法に通常含まれる物質、例えばヘパリン、ヘパラン硫酸、デルマタン硫酸およびコンドロイチン硫酸などのみならず、目的にかなった複数を含すこれらの物質の断片および複数体をも包含することを意味する。

グリコサミノグリカン類の性質として実質的に挙げられるのは、そのポリマー鎖はもろんのことながら、当該一物または二物以上のグリコサミノグリカンの結合は、少なくとも半活性の生出活性を失くさないであるという意味において、質的に生物学的に不活性であるべきである。容易に溶解されるように、複数のグリコサミノグリカン類の結合を可逆とするために、そのポリマー鎖は接頭部に沿って分布され、そして往々に行われる就性度は通常または結合配列を介してグリコサミノグリカンに結合される多くの官能基例えばアミノ、ヒドロキシルまたはカルボキシル基などを有すべきである。ここで注意すべきは、当該グリコサミノグリカンがその調製方法によつては、依然として、その天然複合タンパク質のそれに結合した末端残基を有している可能性があり、その場合結合はもろんのことながら有利なことにかかる基質中の例えばアミノ酸を介して行われるものである。

さらに、特にポリマーは好ましくは良好な水溶性を有するべきである。少なくともそれは、該基質について既述されたところに従つ

て、グリコサミノグリカン類の結合後、少なくとも実質的に水溶性であるべきである。本発明の目的に適する特定のポリマー鎖は一枚の架橋装置により当該者には容易に明らかとなろう。もちろんのことながら、「実質的に複数の」という表現の範囲内で許容されるポリマー鎖上の分子についてもこのことがいえる。

しかしながら、好ましくは、ポリマー鎖は天然または合成のポリペプチド、多糖体または脱脂蛋白質ポリマーである。各端の例としてはポリリジン、ポリオルニチン、キトサン、ポリイミン等およびポリアリルアミンが挙げられる。

グリコサミノグリカンがポリマー鎖に結合した後もその生物学的活性を維持することが通常望ましいという点については、各グリコサミノグリカン分子を例で、そして単純化のみにより複数ポリマーに結合することが望ましい。何切には、グリコサミノグリカンはアミノ酸、尿素または尿素アミノ酸を介して結合されるが、グリコサミン型の遊離アミノ酸を用いてもよい。後者は、それ自身溶解性状態で存在していてもよく、あるいは脱脂酸または脱アセチル化を通過させててもよい。

ポリマー鎖1例あたりのグリコサミノグリカン残基数は、前述のとおり少なくとも20であるが、好ましくはそれより多く、通常は少なくとも30である。該体に付す調節剤から明らかのように、使用ポリマー鎖鎖によつては、ポリマー鎖1例あたりのグリコサミノグリカン残基数は少なくとも60および100以上であつてさえも好ましい場合がある。上段に状況に依存し、そして、特に、選定された固体ポリマーの溶解性、許容される粘度の大きさなどによって設定される。グリコサミノグリカン複数の重複は、特定の複合体の

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巻きされる角に加え、樹脂ポリマーは、にそのサイズにもはける。逆で伸ばされる、複合体の基材表面への接着結合の組合には、もちろん、第2表面の電荷密度も考慮しなければならない。尚って、それらグリコサミノグリカン残基は、結晶に干渉しあうほどに遠近した位置にあるべきではなく、さりとて、それらの間のギャップを広すぎないようにすべきである。一例として、例えば樹脂ポリマーとしてのポリリジンが約10,000より高い分子量を有する例が挙げられる。しかしながら、さきの条件の樹脂ポリマーおよび用途をそれぞれに適したグリコサミノグリカン残基は基質により容易に決定されよう。

特にアミノ-硫酸基を結合として用いる場合、場合によっては樹脂ポリマー主鎖がグリコサミノグリカン類によってまばらにしか遮蔽されない場合には、残った氨基アミノ基をブロックするのが好ましいことがあり。そしてこれは例えばアセチル化によって行われ得る。別の選択法としてのアプローチとして、所要数のアミノ基を例えばメチル基で置換してからグリコサミノグリカン類を結合させることも可能である。

既に示したとおり、本発明による新規複合体は、接着部に対する（通常はそうであるが、必ずしもグリコサミノグリカン残基に対してではない）アフィニティーを有する表面に適合してよく、それにによって表面に所要の生物学的活性を付与することができる。本発明の異なる観点によれば、このような複合表面は、多段の官能基をポリマー主鎖に沿って分布させた幾何学的に離れた官能ポリマーであって、それら官能基を分して強化グリコサミノグリカン残基からの多数の分子が複合体により結合されているものより成る生物学的

に活性な複合体を適切な条件下に、複合体に対するアフィニティーを有する表面と共に接觸させることによって形成される。

本発明のもう一つの観点は、多段の官能基をポリマー主鎖に沿って分布させた実質的に離れた官能ポリマーであって、それら官能基を介して強化グリコサミノグリカン残基からの多数の分子が複合体により結合されているものより成る生物学的に活性な複合体を提供する。

複合体を基材表面の間の長いアフィニティーは静電的性質を有するものであり、そしてより詳細にはその結合は後でより詳しく説かれるように、グリコサミノグリカン残基と基材表面の間の静電的相互作用によって生じる。

本発明による複合体のグリコサミノグリカン分子は樹脂ポリマーに対し大過剰なので、この複合体は“巨大分子グリコサミノグリカン”と考えてよい。そのため、複合体1個あたりの陰イオン基数は、グリコサミノグリカン1分子あたり存在する数をはるかに上回り、その結果、複合体はそのサイズの故に、イオン性相互作用を通して陽イオン性表面に不可逆的に結合することができる。複合体を表面から剥離させるには、もちろんすべてのグリコサミノグリカン残基を同時に表面から剥離させる必要があるが、それには、“逆離”グリコサミノグリカン分子の表面に比べて相当なエネルギー供給が必要となる。

後述するある種の状況を除けば、複合体の生物学的活性はグリコサミノグリカン残基によるものと、一般的に考えられる。このような場合には、グリコサミノグリカンの数は、1個体ポリマー1個あたりのこれらの残基の一部が典型的に陽イオン基が付与されている基

面に対する強度で不可逆的な結合を付与する一方、残りのグリコサミノグリカン残基が生物学的無効、例えば血凝の成分と相互作用することによりその生物学的活性を自由には発揮できるようにするために十分なものとすべきである。

前記によるグリコサミノグリカンを用いた表面開拓は、従って、共有結合とイオン性相互作用の組合せに基づくもので、このことは複合体が中間生成物として解離される（このことはすべての結合化學操作を最終生成物とは別個に行なうことができることを意味している）点で非常に有利である。更に、最終的な表面活性性プロセスが極めて簡単となり、また異常性よく行なうことができる。従って例えば本発明によるヘパリン結合体を用いた表面へヘパリン化は、前述したとおり、従来からの表面へヘパリン化方法に比べて表面に簡便化された効率的ヘパリン化方法を実現する。以上の記載にかかるらず、もちろん、複合体を複合表面にアフィニティーを有させた後で接着工場を所定により行ってヘパリン化表面の安定性をなお一段と向上させることもできる。

従って本発明のこの特徴の観点に従って用いるための複合体は、反対荷電基材表面への実質的に不可逆的な結合を可能にするのに十分な親水架橋機能を有することになる。

前記に述べた表面-開拓、例えば表面-ヘパリン化すべき基材材料は、その表面が陽イオン性であるが陰イオン性にすることができる限り、基本的にはイオコンバブル化が望まれるいざれの材料であってもよい。所定のとおり、本発明は生体にあって異物である材料、例えば各種ポリマー、高聚物およびセラミックスなどに適用することができる。しかしながら、本発明は生体材料、すなわち当該

グリコサミノグリカンに対するアフィニティーを示す複合表面を適用することもできる。これに開拓して、初級に対して最終的構造の走査熱電顕像が走査顕微鏡を有する強化グリコテミノグリカン類を含んでいる点に注目すると興味深い。

基材表面を陽イオン性にするための各種方法がよく知られている。後述する実施例に記すように、ポリイミンによる処理が適切な方法であることが判明しているが、他のポリアミン、例えばポリリジン、キトサンまたはポリアルギニンなどを用いててもよい。

新規なグリコサミノグリカン複合体は、本発明の範囲内において、グリコサミノグリカン類のほかに一またはそれ以上の他の官能、例えば別の生物学的には活性官能の基を担体ポリマーに結合して有してもらよい。その場合、そのような他の生物学的に活性な物質は、グリコサミノグリカン残基と同時にあるいは別々に作用するようにしてよい。後者の場合には、担体表面の生物学的活性だけが興味対象となり、グリコサミノグリカン類だけが基材表面に対するアフィニティー結合に利用される。従って、本発明による複合体は表面に結合せたい所定の生物学的活性のための担体としても適切である。グリコサミノグリカンに加えてポリマー主鎖に結合し得る物質は、反応性モノマー、アルカリ、マトリックス、タンパク質、ステロイドなどである。この文脈においても、極めて特異的な吸着特性を有する複合体を、例えばグリコサミノグリカン単位に対する相補性(complementarity)としてのモノクローナル抗体を用いて得ることができる点に注目すべきである。

別途により、かかる複合せ複合体の場合には、グリコサミノグリカンを有する生体の生物学的活性を抑制したい場合があるが、これは測

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かの異なる方法によって行うことができる。

すなわち、グリコサミノグリカンは、例えば、US-A-4,612,565に記載の方法により調製された末精に位置するアルデヒド基を有する低聚糖分離グリコサミノグリカンを用いてアミノ官能性ポリマー鎖に結合させることができる。しかしながら、この方法は部分分離グリコサミノグリカンに固定され、また置換度の測定が困難である。さらにはまた、ポリマーがブリコサミノグリカンによって比較しやすいことから実験上の特徴も生じる。

併ましい方法によれば、代わりにグリコサミノグリカン結合剤、例えばヘキロニ官能性のものによりポリマー鎖に結合する。しかしながら、例えばヘキロニカルまたはアミノ基に対する二官能性結合剤は、それぞれ分子内および分子間効果を強く結果プロッキンゲン効果を示すので、一般的に使用し難い点に注意する必要がある。

ここで、本発明による結合剤をどのようにしたら調製できるかについての一例として、ポリリジンへのヘパリンの結合を例に説明する。400,000を超える分子量を有するポリリジンを調製することにより1個体分子あたり500個までのヘパリン鎖を有する合成ブロックポリリジンを調製することができる。この目的に適したヘテロ-二官能性結合剤であるN-スクシンイミドカルボ-（2-ビリジルジオ）-ジロビオホート（SPDP）をポリリジン上のアミノ基に結合し次にそのSPDP-置換リジンをクロマトグラフィーにより精製する。別の結合剤でSPDPは、末端アミノ酸残基中にあるいは過剰グルコサミンとして存在するヘパリン上のアミノ基（後者の中量はN-硫酸化またはN-脱アセチル化により調節することができる）

えばヘパリンの結合結合剤の場合には脱硫酸化により行うことができる。従って、このような場合、結合体の生物学的活性は、ポリマー鎖に結合される粗略物質の活性に完全に結合することになる。

多くの場合に、必要とはいわないまでも重要なのは結合体の表面結合作用であるが、この作用は場合によってはさほど重要ではなく、通常によってそれを多かれ少なかれ完全に抑制したい場合でさえあり得る。同様にして、結合結合剤について同様にしたように、純粋なグリコサミノグリカン結合体の場合にもグリコサミノグリカン鎖の生物学的活性を除去するかまたは少なくとも低下させたい場合があり得る。場合によっては、例えばヘパリンについては、グリコサミノグリカンがいくつかの異なる生物学的作用を持つことがあり、そして考慮する角度に応じて一方の生物学的活性を他方を優先させるべく抑制することができる。例えばヘパリンの場合には、その抗凝固作用を前述のとく脱硫酸化により復活する一方、前述の置換度により抑制されない他の生物学的活性は影響されずに保たれるようになることができる。

従って、以上より明らかなるように、新規結合体の研究は、確かな応用分野に基づきやすく直ちに元請にあたり変更させることができると。

本発明のもう一つの観点は、多數の官能基をポリマー主鎖に沿って分布させた実質的に純粋の有機ポリマーを提供し、それら官能基に所定により結合剤によりその非結合部分の硫酸化グリコサミノグリカン鎖から多数の分子を非結合的に結合させることによる酵母結合体の製造に関する。これは本発明の発明においていくつ

にも結合される。SPDP-導入チャーチル官能基に還元剤、SB-置換ヘパリンをクモマトグラフィーにより精製する。ポリリジン中のSPDP基およびヘパリン中のSH-基の含量はそれぞれ分光光度法により測定され、そしてヘパリンとポリリジンとをSPDPおよびSBに加え導入剤を用いて混合し、ヘパリンはジスルフィド交換を介してポリリジンに共有結合的に結合されるが、その反応速度は、分光光度法により測定することができる。驚くべきことに、ポリリジンはSPDP基が付与されている場合には、ポリリジンのアミノ基のほんの一端しか複数されていないかも、ポリリジンとヘパリンの間の反応度が起こらないということがわかった。にもかかわらず、実際の実験は、ジスルフィド交換が高品質度（通常には3M NaCl）においてのみ、より迅速でありて完了まで進行することを示している。反応完了後、結合体をクロマトグラフィーにより精製して粗離ヘパリンおよび分子量低分子物質を除する。

様々な場面でこのように調製されたヘパリン結合体の实用性に關し、驚くべきことに、ヘパリンをポリマー主鎖に結合する被られたジスルフィド橋は、グルタチオンで切断できず、長分子量低分子物質をオール脱去、例えばメルカプトニシノールなどでのみ切断し得ることがわかった。

更に、本発明によるヘパリン結合体へヘパリン化することの実質的意義は、既存方法よりも加工度の低いヘパリン原料から出発されることにある点に注目すべきである。

本発明を如く以下の実施例で詳説する。

実施例

結合体の調製および表面-結合生物学的活性試験

二つの異なるバッテーのヘパリン（ヘパリン、Roche Pharmacis AB社、スエーデン、分子量約12,000）を用いた。アミノ酸含量および過剰第一級アミノ基の相対的存在を分析し、次の結果を得た。

	アミノ酸含量 (%)	過剰量 (%)	第一級アミン (相対的過剰)
ヘパリンA	0.36	3.25	5.000
ヘパリンB	0.08	3.87	340

ヘパリンBの示す過剰アミン含量が極めて低いことから、Yoko Inoue et al., Carbohydrate Research, 46(1976)87-95に記載の方法によるN-脱硫酸化を行った。N-脱硫酸化実施後、第一級アミン相対的目盛りで18,000という値が得られた。

ヘパリンAとヘパリンB（脱硫酸化物）をリン酸緩衝液、pH 6に溶解し（200mg/4ml）、それに1.0gのSPDP（10mg/ml DCCD）を混合して加え、そして反応を20分間進行させた。このようにして得られたSPDP-置換ヘパリンをSephadex G-25（Pharmacia LAB Biotechnology AB社、スエーデン）で精製した。100mgの得られた結合物に500mgのジオタクトレイト（DTT, 10mg/ml）を加え、そして得られる脱壳度を340で分光光度法により測定した。ヘパリンAについての脱壳度は0.25であり、またヘパリンB（脱硫酸化物）については0.17であった。ヘパリンに結合したSPDPはDTTを添加後クロマトグラフィーにより精製することによりSBまで選別した。

450,000の分子量を有するポリリジンを水に溶解し（200mg/3ml）、そこに2.0gのSPDP（10mg/ml DCCD）を加え、そして反応を放置しながら20分間進行させた。精製はSephadex G-25（Pharmacia LAB

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Biochemistry 48社、スニーデン)で溶出剤として0.16M NaClを用いて行った。空隙(void)部分をDITで洗浄し、置換度はポリリジン1分子あたり158 SPDP基を測定された。

以上において調製されたそれぞれヘパリン-SHおよびポリリジン-SPDPの混合を3M NaClに溶解し、そしてSPDP基に対し銀塩が10%過剰となるような順序で混合し、そして反応を一夜進行させた。その結果得物(ヘパリンとおおむねヘパリン日(脱酰胺化物))は完了するまで用意していたが、これはオキシビリジンの過剰を24時間で分光光度法により測定された。それら細胞物をSephadex G-500 (Pharmacia LKB Biotechnology 48社、スニーデン)で0.5M NaClを溶出液として用いて精製したところ、ヘパリン・ポリリジン複合体は過剰ヘパリンに対するペースライン分率を有する充電ピーカとして認められる。ヘパリン含量はLerasorb, R. et al., *Biometrika* 76 (1989) 511-516に記載のオルムノールアセイ法により測定した。

次にそれぞれのヘパリン複合体を0.5M NaClを添加したクエン酸緩衝液、pH 8中で50mgヘパリン/μlまで希釈した。ポリエチレン(PE)チューブを次のような順序により表面へヘパリン化した：

- 1) 過酸化アンモニウム(1%, 60°C, 120分間)
- 2) ポリエチレンイミン(0.3g/μl, 室温, 15分間)
- 3) 前段のぬき混合液体浴槽(室温, 120分間)

それらチューブを最後に、ホウ酸緩衝液、pH 9で2×10分間および水で洗浄した。

表面-ヘパリン化チューブを次の方法によってトロンビンの吸着液に関して試験した。それらチューブはまずヒト血漿と共に形成さ

せた後、それらを塩化ナトリウム溶液で洗浄した。次にそれらチューブをトロンビンの希釈と共にインキュベートし(15μl/μl, 10分間、室温、暗室)そして塩化ナトリウム溶液で洗浄した。次にそれらチューブの半分をフィブリノーゲン除去した血漿と共に50秒間インキュベートした。表面-結合トロンビン活性は、それらチューブをトロンビンの濃度を基準と共に60秒間インキュベート後反応をクエン酸緩衝により止めることにより測定した。得られる吸光度を405nmで測定した。次の値が得られた。

	ヘパリンA (未処理 との比較)	ヘパリンB(脱酰胺 化物)との比較
トロンビン活性 (フィブリノーゲン 除去液素不使用)	0.639±0.030	0.611±0.166
トロンビン残存量 (フィブリノーゲン 除去液素使用)	0.003±0.001	0.006±0.001

この結果は、いずれの調製物もトロンビンの活性および阻害に同じ完全に満足できる効果を与えることを示している。

実験例2

各種凝固液を有する複合体および表面結合生物学的活性試験複合体1と呼ばれる複合体を発泡鋼の記載と同じにして調製した。ポリリジン1個あたりのヘパリンの活性度は240±1であった。

次に複合体1と呼ばれる別の複合体を調製した。この場合の出発材は、SPDP基の前にポリリジンが液中のpHを8に調整することにより調製された、より高いSPDP置換度のポリリジンであった。その置換度は1ポリリジン分子あたり0.33 SPDP基と測定された。

ヘパリン-糊を実験例1と同じにして調製し、そして前記において得られた高置換度のポリリジンと反応させた。反応は77%活性まで進行し、述べて、ポリリジン1個あたりのヘパリンの置換度は690:1であった。ポリエチレン(PE)のチューブを実験例1の記載と同様に調製し、試験して、次の結果が得られた。

	未処理	混合体B
トロンビン活性 (フィブリノーゲン 除去液素不使用)	0.516±0.021	0.526±0.021
トロンビン残存量 (フィブリノーゲン 除去液素使用)	0.011±0.001	0.008±0.001

これらの結果はいずれの複合体も満足できる結果を与えることを示している。

実験例3

表面-ヘパリン化体外システムの試験

次の成分で被覆される外シス템を用いた・硝酸(ドナーサ)カーテル(ポリ塗装ビニル(PVC))・硝酸カーニューレ(PVC+ステール)、チューピングセット(PVC)、ポンプ部(エチルアルチアクリレート)、加(ポリプロピレン(PP)+PB)、離乳介育器(ポリカーボネート+PEの空隙板)。

それらすべての構成を三工程処理により表面-ヘパリン化した：

- 1) 過酸化アンモニウム(1%, 60°C, 120分間)
- 2) ポリエチレンイミン(0.3g/μl、ホウ酸緩衝液、pH 9、室温、15分間)
- 3) 洗浄液¹に用いて調製されたヘパリン・ポリリジン複合体を、

0.5M NaCl含むクエン酸緩衝液、pH 8中、30μl/μlまで希釈し、そして室温で120分間処理した。前記液を最後に、ホウ酸緩衝液、pH 9および水で2×15分間洗浄した。乾燥後、エチレンオキサイドによる封閉を行った。

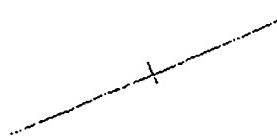
この外側システムを右心耳と大動脈の間の成分バイパスに対し抗凝固剤液を受け付けてない封閉ブリッジ接続した。この外側システムは、2時間にわたり連続的に約8μl/分をポンプ給送したが凝固による凝血の問題は会くなかった。凝固時間は常に一定量であったが、このことは血栓塞栓へのヘパリン遮断はなかったことを示している。

これらの結果は、体外リガード装置用の完全システムをヘパリン複合体で表面-ヘパリン化することにより、エチレンオキサイドで封密できる、安全で十分機能するヘパリン表面を得ることができる事を実証している。

実験例4

穿刺液中の各種ヘパリン-結合体の生物学的活性の試験

様々な置換度を行するヘパリン-ポリリジン複合体を実験例1および2に用いて調製した。複合体の生物学的活性を、次トロンビン活性緩衝液中または血漿中ににおける第2相活性およびトロンビン阻害剤について測定した。得られた結果を最初の生物学的活性(100 U/I/μl)を有する低筋度のヘパリンを基準することにより得られる対応率グラフと比較した。次の結果が得られた。



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408(Pharmacia LKB Biotechnology AB社、スニーデン)を分離・体とするカラムで行った。混合体は逆流ヘパリンから分離しなかった。他の混合体については、満足できる分離が得られ、また得られた混合体は、実施例1に従ってチューブを表面ヘパリン化するために用いることができる。(実施例1にはった)トロンビンの活性および吸収に関する結果は次の結果を得た:

生物学的活性 I.U./mgヘパリン					
混合体	ヘパリン/ ポリリジン	IgG/AT	IgG/免疫	Tr./AT	Tr./免疫
I	235	116	95	48	45
II	450	61	29	10	20
III	658	10	43	18	25

それらの結果は、既報のプロセスが無い生物活性および良い生物学的活性を有する混合体の調製に用いることができるこを示している。

実験例1

接着基

様々なポリリジンのサイズの初期
それぞれ13,000、64,000、33,000および404,000の分子
量を有する異なるバッヂのポリリジンを実施例1に従ってSPPDで反
応して、次の直換率(ポリリジン1分子あたりSPPD-基数)が得ら
れた。

基種	分子量	直換率
I	13,000	6
II	64,000	21
III	33,000	45
IV	404,000	35
V	249,000	87
VI	466,000	158

第一級アミンのための端的の目盛りで1,000の値を有するヘパリンを実施例1に従って、逆流オール基を導入するためにSPPDで反
応して、0.2~0.3の直換率を得た。それらの混合体は実施例1に
従って調製した。分別は、Sephadex® G-300またはSephadex® S-

M-50Gで溶出した。空隙部分を除め、そしてSPPDの洗浄について分離した。SPPDの色基は、キトサン1分子あたり約10 SPPD基に相当する0.572nmole/gを測定された。

逆流オール基を有するヘパリンを実施例1に従って調製した。得られたヘパリン溶液に次に催化チトリウムを3.5Mの最終濃度となるように添加した。次にそのヘパリン溶液を最初に調製したキトサン-SPPD溶液に強しく攪拌しながら蒸気化し、そして反応を室温で一夜進行させた。分光光度計測定吸収が100%まで達成したことを見ていた。その溶液をSephadex® G-300(Pharmacia LKB Biotechnology AB社、スニーデン)で分離し、そして空隙分離を始めた。Pegas® (Atchimie社(フランス))のポリエーテルブロックアミド)のチューブを実施例1によるトロンビン試験のために調製した。次の結果が得られた:

トロンビン活性 (フィブリノーゲン 除去血漿不使用)	トロンビン活性 (フィブリノーゲン 除去血漿使用)
0.451±0.016	0.092

これらの結果は、キトサン-ヘパリン混合体を用いて調製された表面が完全に満足できる結果を与えることを実証している。

実施例2

ポリアリルアミンとの混合体の調製

10mgのポリアリルアミン塩酸塩(Aldrich社、分子量約50,000)を1.5mlのホウ酸緩衝液、pH9に溶解し、それに1.0mlのSPPD(10kg/g Reagent)を調節しながら蒸気化し、そして30分間反応させた。その後液をPD-10カラムにかけ、それを0.05%AgNO₃で検出した。空隙部分を除め、そして分別したところポリアリルアミン1分子あたり約102

混合体	トロンビン活性 (フィブリノーゲン 除去血漿不使用)	トロンビン活性 (フィブリノーゲン 除去血漿使用)
I	--	--
II	0.012±0.006	0
III	0.086±0.047	0
IV	0.194±0.009	0.003
V	0.532±0.043	0.000
VI	0.490±0.004	0.004

これらの結果は、混合体I~IVが本発明に従ってヘパリン活性を有する表面の調製に使用できることを示している。しかしながら混合体V~VIが著しい結果を示した。

実施例3

キトサンを基体物質とする混合体の調製

キトサン(SeaCare® 116 L、粘度<20mPa·s、分子量約120,000、Protein Biopolymer AB社、ドラメン(Drammen)、ノルウェイ)を、1%酢酸水溶液に10kg/gとなるよう溶解した。1.5mlの溶液に1.0kgのSPPD(10kg/g Reagent)を50°Cで搅拌しながら添加し、そして反応を1時間進行させた。試料をPD-10カラム(Pharmacia LKB Biotechnology AB社、スニーデン)にかけ、そして1%酢酸水溶液に

SPPD基に相当する8.16nmole/gのSPPDを含むしていることが示された。この生成物を以下において混合体Iの調製に用いた。

別の10kgのポリアリルアミン塩酸塩をホウ酸緩衝液ではなくて水に溶解し、酢酸と同様にしてSPPDを調製した。その場合、空隙部分は、ポリアリルアミン1分子あたり3.5 SPPD基に相当する1.56nmole SPPD/gを含有していた。次いで、この生成物を以下の混合体Iの調製に用いた。

もう一つの調製例では、pH3.5に調整した7mlの水に溶解した2mmoleのポリアリルアミンを1610 mmoleのシアンゴロヒドリドの存在下に861 mmoleのカルムアルドヒドと反応させることにより部分的にメチル化してあるポリアリルアミン塩酸塩が用いられた。一夜反応させた後、液体ポリアリルアミンをSephadex® C-25(Pharmacia LKB Biotechnology AB社、スニーデン)で調製した。

10kgの液体ポリアリルアミン塩酸塩をホウ酸緩衝液、pH8に溶解し、そして前述と同様にSPPDで調製した。その場合、空隙部分はポリアリルアミン1分子あたり約50 SPPD基に相当する1.56nmole/gを含有した。次にこの生成物を以下の混合体IIの調製に用いた。

逆流オール基を有するヘパリンを実施例1に従って調製し、得られたヘパリン-SHをそれぞれのポリアリルアミン-SPPD塩酸塩とSS-およびSPPD基に蒸気化蒸発させた。一夜反応後、混合液を3Mまで高め、そして反応を室温で一夜進行させた。混合体IおよびIIのそれぞれの反応液を10M氷酸化ナトリウムでpH10に調節し、次いで100mlの蒸留水を適しく混合しながら蒸発して残留アミノ基をアセチル化した。得られたヘパリン混合体、複合

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体I、複合体IIおよび複合体IIIをそれぞれSephacryl S-400カラム(Pharmacia LKB Biotechnology AB社、スウェーデン)で精製したところ、複合体は空隙区分中に得られた。

得られた三種類のヘパリン複合体を用いて、実施例1によるトロンビン試験のためにポリエチレンチューブを調製し、次の結果を得た。

トロンビン拘束 (フィブリノーゲン 除外測定不使用)	トロンビン残存量 (フィブリノーゲン 除外測定使用)
複合体I 0.457±0.008	0.001±0.002
複合体II 0.445±0.020	0.003±0.001
複合体III 0.501±0.012	0.005±0.002

これらの結果は、三種類の複合体のすべてが完全に拘束できる効果を与えることを実証している。

実施例8

様々なアミノ酸性基質表面に対する表面の調節

ポリエチレンチューブを次の上にしてヘパリン化した(付された印A、B、CおよびDはそれぞれチューブ表面の別の選択肢としてのアミノ酸性基質処理を示している)：

1. 過酸化アンモニウム(3%、60°C、60分間)
2. ポリエチレンイミン(0.3mg/ml、モレートpH 9、室温、15分間)
3. ポリアクリルアミン(0.5mg/ml、モレートpH 9、室温、15分間)
4. キトサン(10mg/ml、160°C、50°C、15分間)
5. ポリリジン(水1.5ml/ml、室温、15分間)
6. 空隙区分によって調整されたヘパリン-ポリリジン複合体(ク

エン酸塩液中50mg/ml、0.5M NaCl、pH 8.5、室温、120分間)

このようにして調製された表面をカクテル液、pEGFおよび水で十分洗浄した。

前述の四つの選択肢に従ってヘパリン化されたポリエチレンチューブを実施例1に記載された如く、トロンビンの拘束および屠殺について試験したところ、すべての選択肢が完全に拘束できる効果を示した。

実施例9

レンズ(PMMA)の表面へヘパリン化および動小板付着試験

ポリメチルメタクリレート(PMMA)の表面レンズを実施例1に従ってヘパリン化した後、血小板付着について試験した。

無活性化シスおよび表面へヘパリン化レンズをそれぞれ、無活性化剤を含む血中で一定の濃度を含むながら60分間インキュベートした。それらレンズを次に活性ナトリウム溶波中でクリア化をしてすべての付着血波を除去した。最後にアデノシン三リン酸(ATP)をシングル表面に付着したすべての血小板から抽出し、そして得られたATPの含量をバイオラミセансにより測定した。ヘパリン化レンズへの血小板付着は未処理对照レンズに比べ98%低下した。

実施例10

「生物学的表面」へのヘパリン複合体の吸着

本発明により調製されたヘパリン複合体が血栓形成生物学的材料で被覆された表面に不可逆的に吸着されるかどうかを調べるために次の実験を行った：

ポリエチレンカラム表面活性化チューブをクニン液加全血で半分満たして60分間固定させた。次にそれらチューブから血液を出し

て活性化されたヘパリンを添加した(ヘパリン、38ml加量は活性化SPDP基の量も80%に相当するものとした)。反応は完了するまで進行した。得られた複合体を最後にSephacryl S-400カラム(Pharmacia LKB Biotechnology AB社、スウェーデン)で精製したところ、複合体は空隙区分中に得られた。得られた複合体を試験したところヘパリン活性およびリアーゼ活性が検出され得ることが示された。

して活性化ナトリウム溶液で十分洗浄した。ここで前記チューブを様々な活性段階の血小板および血漿タンパク質により成る血栓活性材料で被覆した。実施例1に従って調製されたヘパリン-ポリリジン複合体を活性ナトリウム液波中で100mg/mlの最終濃度となるように希釈し、次にその溶液をそれらチューブ内に60分間固定させた。それらチューブを最後に、ホウ酸緩衝液、pEGFおよび水で十分洗浄した。

このようにしてヘパリン化されたチューブを実施例1に従ってトロンビンの拘束および屠殺について試験したところ、各チューブは完全に拘束できる効果を示した。

実施例11

ケラーゼとの結合性調査

ポリリジン(10mg、分子量40,000)を1.5mlの冰に溶解し、それに0.5mlのSPDP(10mg/ml NaOH)を投漬しながら搅拌し、次に反応を30分間進行させた。その試料をPD-10カラムにかけ、そして0.5% NaClで洗出した。空隙区分を含め、そして分析したところSPDP含量が1.053mol/gであることが示された。

ケラーゼ(IV-1500、クテナタマメ由来、Sigma社、米国)をリン酸緩衝液、pH 7.5に10mg/mlとなるように溶解し、そして0.22×斐氏シラーを用いて透過した。透析SHG合量は0.151mmol/gと測定された。

3M NaClに溶解したポリリジン-SPDPをケラーゼと、利用可能なSPDP基の約10%がケラーゼのSH基とのジスルフィド交換を受けるように混合した。343nmにおける分子光吸收測定によりこれが生じたことが確認された。次に実施例1に従って透析SHG

特許出願の翻訳文提出書
(特許法第184条の8)

平成6年3月25日

特許庁長官

1. 国際出願の表示
PCT/JP 92/00672

2. 発明の名称
新規接合体、その構造および使用ならびにその接合体を用いて調製された基体

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(外2名)

5. 治正書の提出年月日 1993年11月25日

6. 本件発明の冒頭
掲載頁の翻訳文(請求の範囲)
1 頁

7. 説明書
請求項1および2が治正された。

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請求の範囲

- 多數の官能基をポリマー主鎖に沿って分布させた実質的に剛性の有機ポリマーであって、それら官能基を介して硫酸化グリコサミノグリカン類群からの少なくとも約20分子が共存結合を通して結合されそして各グルコサミノグリカンが該グルコサミノグリカンの非活性部分において特異的に単結合を介してポリマー主鎖に結合されているものより成る実質的に水溶性の生物学的に活性な接合体。
- 前記ポリマーが突然または合成のポリペプチド、多糖体または脂肪族ポリマーに由来する請求項1記載の接合体。
- 前記ポリマー端がポリジン、ポリオルニチン、キトサン、ポリイミンまたはポリアリルアミンに由来する請求項2記載の接合体。
- アクリコサミノグリカン類が実質でポリマー主鎖に結合されいる請求項1、2または3のいずれか1項記載の接合体。
- グリコサミノグリカン類が該グリコサミノグリカン類に結合したアミノ基を介したポリマー主鎖に結合されている請求項1～4のいずれかに記載の接合体。
- 接合体がそのグリコサミノグリカン類の端に、水に溶解された場合に実質的にその全長において正荷電基部表面に静電的相互作用により定量的に不可逆的に結合され得るのに十分なポリ陰イオン特性を有することを特徴とする請求項1～5のいずれか1項記載の接合体。
- 少なくとも30グリコサミノグリカン残基を有する請求項1～6のいずれか1項記載の接合体。

- 少なくとも100グリコサミノグリカン残基を有する請求項7記載の接合体。
- 前記グリコサミノグリカンがヘパリンまたはその新片または誘導体である請求項1～8のいずれか1項記載の接合体。
- グリコサミノグリカン残基が結合配列を介してポリマー主鎖に結合される請求項1～8のいずれか1項記載の接合体。
- 前記結合配列がヘテロ・二官能性結合試薬に由来する請求項10記載の接合体。
- ポリマー主鎖がグリコサミノグリカン類のほかに少なくとも一つの附加的な生物活性に活性な供給の残基を有する請求項1～11のいずれかに記載の接合体。
- 接合体が多數の官能基をポリマー主鎖に沿って分布させた実質的に剛性的官能ポリマーであって、それら官能基を介して硫酸化グリコサミノグリカン類群からの多數の分子が共存結合を通して結合されているものより成り、該接合体は好ましくは該接合体と基体表面との間の静電的相互作用により表面に結合されていることを特徴とする。表面にアフィニティー結合された生物学的に活性な接合体より成る調製された基体装置。
- 生物学的に活性な接合体が請求項1～11のいずれかに記載の接合体である請求項13記載の調製された基体装置。
- 多數の官能基をポリマー主鎖に沿って分布させた実質的に剛性的官能ポリマーを準備し、そしてこれら官能基に、別途により粘合剤を介して、その非活性部分の硫酸化グリコサミノグリカン類群からの多數の分子を共存結合的に結合させることより成ることを特徴とする。硫酸アグリコサミノグリカン類群からの多數の分

- 子を提供する実質的に剛性的官能ポリマーより成る生物学的に活性な接合体の調製方法。
- 多數の官能基をポリマー主鎖に沿って分布させた実質的に剛性的官能ポリマーであって、それら官能基を介して硫酸化グリコサミノグリカン類群からの多數の分子が共存結合を通して結合しているものより成る接合体を該接合体に対するアフィニティーを有する基体表面と、接合体がそこに実質的に不可逆的に結合されるように接觸させることを特徴とする、硫酸化グリコサミノグリカン類による表面の調製方法。
- 接合体がポリ陰イオン特性を有し、基体表面が陽イオン性である請求項16記載の方法。
- 治療剤として用いるための請求項1～12のいずれか1項記載の生物学的に活性な接合体。

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特許庁長官　伊藤山　英　志

1. 補正の内容

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2. 修正する箇

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4. 補正の各の件名(略記)

5. 補正登録者姓名

伊藤山　英　志

6. 補正登録項目名

明細書、請求の範囲

7. 補正の内容

1) 請求の範囲を引抜のところを修正します。

2) 取扱説明書第14行の「左側された後」を「右側させた後」と修正します。

3) 図表9表下から6行の「そのも」を「もの」と修正します。

4) 図表12表下から6行め「複イオン性であるか」を「四イオン性であるか、または」と修正します。

以上

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請求範囲

1. ポリイソブチル、ポリオルニチン、多糖体および脂質成形ポリマーからなる野より活性されそして化学反応性あるポリマーを特に用いて有効させた実質的に粘度の有効アリマー形態での生物学的に不活性な酵母、およびそれらの化学反応性に活性部位を介して結合された少なくとも30分子の脂肪酸グリコサミノグリカンからなる低トロンビン活性を有する水溶性化合物であり、ここで
該脂肪酸グリコサミノグリカン分子は、改質化アリコサミノグリカン分子が半胱氨酸側鎖に結合した後に改質化アリコサミノグリカン分子が低トロンビン結合活性を保持するように、低トロンビン結合活性に活性のないその分子の部分中の一つの結合点を介してポリマー主鎖に結合していることを特徴とする低トロンビン結合活性を有する水溶性化合物。
2. 特異的に強烈な有効ポリマー組成がオリゴシン、ポリオルニチン、キトサン、アリイシンまたはポリアリスチンである請求項1記載の化合物。
3. 改質化アリコサミノグリカン分子のいくつかまたは全てが、複数改質アリコサミノグリカン分子の水溶液を介してポリマー主鎖に結合されている請求項1または2に記載の化合物。
4. 改質化アリコサミノグリカン分子が、改質化アリコサミノグリカン分子のアミノ基を介してポリマー主鎖に結合されている請求項1記載の化合物。
5. 少なくとも100個のアリコサミノグリカン分子を有する請求項1記載の化合物。
6. 改質化アリコサミノグリカン分子がヘパリンまたはその誘導体である。

本件の記載の化合物

7. 改質化アリコサミノグリカン分子が結合試薬を介してポリマー主鎖に結合している請求項1記載の化合物。
8. 結合試薬がヘキロニニ酸結合試薬である請求項7記載の化合物。
9. 実質的に粘度の有効アリマー組成、そのポリマー主鎖に結合する少なくとも1つ以上の活性部位を有する低トロンビン活性を有する水溶性化合物。
10. 請求項1または2に記載の主鎖に記載の水溶性化合物および半胱酸側鎖に活性な有効の結合試薬。
11. オリゴシン、キトサン、多糖体および脂質成形ポリマーからなる野より活性されそして化学反応性あるポリマーを特に用いて有効させた実質的に粘度の有効アリマー形態での生物学的に不活性な酵母、およびそれらの化学反応性に活性部位を介して結合された少なくとも30分子の脂肪酸グリコサミノグリカンからなる低トロンビン結合活性を有する水溶性化合物であり、ここで
該脂肪酸グリコサミノグリカン分子は、改質化アリコサミノグリカン分子が半胱氨酸側鎖に結合した後に改質化アリコサミノグリカン分子が低トロンビン結合活性を保持するように、一つの結合点を介してポリマー主鎖に結合している上記を有する化合物において、
ヘキロニニ酸結合試薬を改質化アリコサミノグリカン分子およびポリマー主鎖のカルボン酸上では半胱酸側鎖と反応されることからなるが、日本は改質化アリコサミノグリカン分子との活性化反応活性との反応が、低トロンビン結合活性に活性のない改質化アリコサミノグリカン分子が結合して行われるかで特徴とする請求項6記載の化合物。
12. 低トロンビン結合活性化合物が、ポリマー主鎖に沿って分布させた旨

化合物を有する実質的に粘度の有効アリマー組成がそれらの日経通じて有効性を有して結合された少なくとも30の改質化アリコサミノグリカン分子からなることを特徴とする。具体例にアラニン側鎖された低トロンビン結合活性化合物からなる新規化合物。

13. ポリマー主鎖に沿って分布させた化学反応性を有する実質的に粘度の有効アリマーのポリスイオントドクタ、および化学反応性に活性部位を介して結合された少なくとも30の改質化アリコサミノグリカン分子を、低トロンビン結合活性に活性のない改質化アリコサミノグリカン分子の部分中の一つの結合点を介して、ポリスイオントドクタに介してアリニテーを有する低トロンビン結合活性と、低トロンビン結合活性が強度的に活性部位によりは低トロンビン結合活性に結合されるように構成せられた二重からなる、改質化アリコサミノグリカンによる表面の複数方法。